THE EFFECT OF CARDIOPULMONARY BYPASS ON RESPIRATORY FUNCTION IN MAN

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Abstract

The change in pulmonary function which follows cardiopulmonary bypass (CPBP), as practised with modern techniques, was evaluated in 10 patients undergoing coronary vein-graft operations. Measurements were made during the week before operation and on 5 occasions postoperatively.

The study was preceded by an attempt to establish normal values for pulmonary blood-gas exchange, in the supine position. It proved impracticable to predict the normal range of alveolar-to-arterial oxygen tension difference (ΔAaP_{O_2}) and venous admixture ($\dot{Q}va/\dot{Q}t$), when supine, according to age. The relationship of closing volume (CV) to expiratory reserve volume (ERV) was important in determining these and was not closely related to age.

In the CPBP study, mean $\dot{Q}va/\dot{Q}t$ breathing air, increased from 9.59% to a maximum of 13.71%, 22 hr postoperatively. Mean $\dot{Q}va/\dot{Q}t$, breathing oxygen, increased from 7.02% to a maximum of 15.71%, 48 hr postoperatively. Most of the deterioration in gas exchange appeared to be due to increase in regions of lung with no ventilation or with critically low ventilation/perfusion ratio ($\dot{V}/\dot{Q}$). These changes were no greater than those reported to follow upper abdominal operations without CPBP though this comparison is difficult to make because of technical and other differences. None of the preoperative tests afforded a reliable forecast of the postoperative venous admixture. Arterio-venous oxygen content difference ($\Delta a\bar{v}C_{O_2}$) had risen significantly by 22 hr and was still raised at 48 hr. This probably indicates an abnormal cardiac output in this period. Ten days postoperatively $\dot{Q}va/\dot{Q}t$ and $\Delta a\bar{v}C_{O_2}$ had returned to the

preoperative level.

Despite an attempt to select subjects whose lung function was normal before operation, there was variation not only in their preoperative clinical state but also in their postoperative clinical course. These variations may have accounted for some of the differences in physiological behaviour. Conclusions drawn from the mean values above should, therefore, be applied with caution in other circumstances. The group is, however, likely to be representative of the fittest patients having cardiac operations with CPBP at Green Lane Hospital.

To Barbara and my mother and father.

Acknowledgements

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Declaration

This thesis has been composed entirely by me. I have been in charge of a group carrying out the work. The experimental designs have been mine and I have carried out many of the technical procedures and all the analysis of results. The methods of gas and blood-gas analysis have been established by Dr. E.A. Harris in the Clinical Physiology Department at Green Lane Hospital. This thesis has been specially written for the degree of Doctor of Medicine in the University of Edinburgh and has not been submitted for any other degree, diploma or professional qualification.

Material from the first part of this thesis has been published in the American Review of Respiratory Disease, Volume 115, 1977, page 571. A paper describing some of the results from Part II of the thesis has been published in the Journal of Thoracic and Cardiovascular Surgery, Volume 75, Number 1, January 1978, page 104.

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Symbols and abbreviations

$\dot{V}$, gas volume per unit time e.g. $\dot{V}_{O_2}$, O_2 consumption per min.

P, gas pressure

F, fractional concentration

f, respiratory frequency

R, respiratory gas exchange ratio

$\dot{Q}$, volume fo blood per unit time e.g. $\dot{Q}_t$, total blood flow or cardiac output per min.

C, concentration of gas in blood phase

Subscripts

I, inspired gas e.g. $F_{I_{CO_2}}$ fractional concentration of CO_2 in inspired gas

E, expired gas

A, alveolar gas e.g. $\dot{V}_A$ alveolar ventilation per min.

T, tidal gas e.g. V_T tidal volume

D, dead space gas e.g. V_D, volume of dead space gas

a, arterial blood

$\bar{v}$, mixed venous blood e.g. $C_{\bar{v}O_2}$, ml O_2 per unit volume of mixed venous blood

$\acute{c}$, end capillary

Compound symbols

$\Delta AaPO_2$, alveolar-to-arterial O_2 tension difference

$\Delta a\bar{v}C_{O_2}$, arterio-venous O_2-content difference

$\dot{Q}_{Va}/\dot{Q}_t$, venous admixture, per cent of cardiac output

$\dot{V}/\dot{Q}$, ratio of ventilation to perfusion

Lung volumes

VC, vital capacity

ERV, expiratory reserve volume

FRC, functional residual capacity

RV, residual volume

TLC, total lung capacity

CV, closing volume

CC, closing capacity

SRaw, specific airways resistance

Partial pressures of O_2 and CO_2 in blood are expressed in mm Hg as these are the units in which they were read and the units which are used at Green Lane Hospital.

Introduction and objectives

The Cardio-Thoracic Surgical Unit at Green Lane Hospital in Auckland was founded by Sir Douglas Robb in 1942. He seems to have had a great deal of help and encouragement from the chest physicians Dr Chisholm McDowell and Dr John Hinds. The first operation using cardiopulmonary bypass at Green Lane was performed by Sir Brian Barratt-Boyes in 1958. Since then over 5,000 bypass operations have been done and the unit has acquired an international reputation. Coronary vein-graft surgery began at Green Lane in 1969 and since then some 800 such operations have been done there. Thus, Green Lane Hospital was an excellent place to conduct a study of the effects of cardiopulmonary bypass on respiratory function.

Work published in the nineteen-sixties indicated that gross changes occurred in pulmonary function following surgery using cardiopulmonary bypass (CPBP). The clinical course of many patients tended to confirm the impression and some studies suggested that the deterioration in lung function was greater than might be expected to follow surgery of similar degree without bypass. However, continual change in bypass technique and the wide variation in the pulmonary status of patients coming to bypass surgery has made comparison of lung function changes between different groups of little value.

More recently many patients are undergoing coronary vein-graft surgery. A considerable number of these seem to have no physical disabilities other than angina. It seemed that these patients might provide a group who could be easily matched with respect to age, heart function, smoking and

preoperative pulmonary function, and a study of their post-operative lung function might be of considerable value as a baseline for future comparative studies. It seemed valuable, therefore, to study such a group to establish values for the minimal deterioration to be expected in lung function following bypass using modern techniques.

It was hoped such a study would provide:-

(1) A measure of the minimal change expected in pulmonary function following cardiopulmonary bypass as practised at Green Lane Hospital in 1976.

(2) A yardstick by which to judge benefits (in pulmonary function) of future changes in bypass technique.

(3) Perhaps some insight into the mechanisms producing the deterioration in lung function.

(4) An indication of which preoperative tests marked those at special risk from pulmonary complications.

(5) A baseline with which to compare pulmonary changes produced in other groups e.g. a) those with severe valve disease and abnormal pulmonary function preoperatively, b) a group having major surgery without bypass.

With these objectives in mind, a detailed evaluation of respiratory function was carried out in 10 patients having coronary vein-graft surgery and preoperatively almost normal lungs. Because the operative study would require measurements in the supine position, and because there are few good studies in healthy subjects in which ΔAaP_{O2}, $\dot{Q}va/\dot{Q}t$ and physiological dead space (V_D) have been measured in that posture, it was decided to precede the bypass study with a study of pulmonary blood-gas exchange in healthy volunteers. It was hoped that this study

would provide a set of normal values for gas exchange supine and thus the means of assessment of the normality of the patients entering the surgical study and a better indication of the degree of abnormality after operation. It was also hoped that the study would provide information about the mechanisms producing changes in gas exchange due to alteration in posture. Twenty-four normal subjects aged 20-72 yr, therefore, had pulmonary blood-gas exchange assessed, sitting and lying, breathing air and oxygen. Particular attention has been paid to the role of airway closure in the production of $\dot{Q}va/\dot{Q}t$. The preliminary study of normal supine gas exchange is the subject of Part I of this thesis.

The second part of the thesis deals with the 10 patients having coronary vein-graft operations. Measurements of respiratory function were done during the week before operation and on up to 5 occasions afterwards. Postoperative studies were attempted at approximately 8 hr, 22 hr, 28 hr, 48 hr and 10 days. The matching of pulmonary ventilation and perfusion was assessed in terms of the three-compartment model, with steady-state measurements of arterial gas tensions (radial artery catheter), pulmonary-artery gas tensions (pulmonary artery catheter), haemoglobin, oxygen saturation, mixed expired gas concentrations and volume (Douglas-bag collection). Patients were studied breathing air and oxygen. Alveolar-to-arterial oxygen tension difference, $\dot{Q}va/\dot{Q}t$ and V_D were derived. Cardiac output ($\dot{Q}t$) was calculated from measured $\Delta a\bar{v}C_{O_2}$ and oxygen uptake ($\dot{V}O_2$). Nitrogen-clearance index was measured as the subjects were changed from air to oxygen breathing and functional residual capacity (FRC) calculated from the washout trace. Lung volumes, airways resistance (Raw) and closing volume were measured preoperatively.

PART I

The Effect of Posture on Venous Admixture and Respiratory Dead Space in Health

Introduction

It was important to know if the patients going forward to coronary vein-graft surgery had normal lung function preoperatively. As the postoperative studies would be performed with the patients supine, for comparison, their preoperative tests would have to be done in the same position. A review of the literature showed that there are few accurately measured values for normal blood-gas exchange in the supine position. Thus assessing the preoperative results would have been difficult. It was, therefore, decided to try to establish a set of normal values for ΔAaP_{O2}, $\dot{Q}va/\dot{Q}t$ and V_D, supine, breathing air and oxygen. By setting standards for blood-gas exchange in the lying position it would also be possible to assess, more accurately, abnormalities after operation. This study would provide a chance to examine the factors producing alterations in gas exchange, associated with a change of posture.

Review of the literature

Objectives

The objectives of the review of the literature were:

1. To look for, accurately measured, normal values for pulmonary blood-gas exchange, supine, breathing air and oxygen.
2. To understand factors likely to alter the distribution of pulmonary ventilation, perfusion, the matching of ventilation and perfusion, and likely to alter cardiac output and arterio-venous oxygen-content difference. The effects of change in posture, increasing age and breathing oxygen on these and the alveolar-to-arterial oxygen-tension difference, venous admixture and physiological dead space were examined.

The literature describing the alterations in pulmonary blood-gas exchange associated with ageing, change of posture and change from air to O_2 breathing is vast. It seems best to make a bold statement of currently held views first and then to look at the evidence for and against these views in the literature.

a. Distribution of pulmonary ventilation

It seems that the major factor determining distribution of pulmonary ventilation at slow rates of breathing is gravity-dependent regional differences in effective compliance. The pleural pressure gradient accounts for different regional volumes, and for differences in relative ventilation and dependent airway closure at low lung volume. Airways resistance seems to affect distribution of pulmonary ventilation only at flow rates greater than 0.5 $l.sec.^{-1}$ Stratified inhomogeneity probably also contributes to uneven distribution of ventilation but is unlikely to be altered much by change in posture.

Regional differences in effective compliance mean that the ventilation of the lung bases is nearly twice the ventilation of the apices in upright normal adults breathing in the tidal range. Less variation in regional pleural pressure in the supine position means that the distribution of ventilation may be more uniform than when upright, at any rate in young people. Despite the fall in breathing level on lying down they are unlikely to have significant airway closure during tidal breathing.

Reversal of the normal pattern may occur with increase in compliance (as in ageing), disease of small airways and at low lung volume, and this is associated with dependent airway closure in the tidal breathing range. Ventilatory pattern is therefore commonly the reverse of normal in people over 65 yr either erect or supine and (due to the fall in breathing level) in those over 45 yr when supine.

Breathing oxygen seems to have little effect on the distribution of pulmonary ventilation.

b. Distribution of pulmonary blood flow

The distribution of pulmonary blood flow is also gravity dependent. The pulmonary circulation is a low-pressure system working in a gravitational field and, in any given lung zone, blood flow depends on the relationship of pulmonary arterial pressure, alveolar pressure and pulmonary vein pressure in that zone. In the upright lung the regional pulmonary artery and vein pressure falls with distance above the hilum and, since main pulmonary artery pressure is normally about 18/8 cm H_2O and the apex approximately 13 cms above the hilum, it seems that pulmonary alveolar pressure will exceed arterial pressure for at least part of the

cardiac cycle, and venous pressure for the whole cycle, at the apex. Lower in the lung there will be a zone in which pulmonary artery pressure exceeds alveolar pressure but alveolar pressure exceeds venous pressure and here flow will depend on the difference in pressure between arteriole and alveolus. In dependent areas flow will be regular and depend on arteriole-to-venous pressure difference. This mechanism accounts for the markedly higher perfusion of the lung bases when upright.

When supine, gravitational differences are less since the antero-posterior diameter of the lung is less than its height and this, with the postural increase in cardiac output, makes the distribution of pulmonary perfusion more uniform when supine than when upright. With ageing, apical blood flow is increased but flow is still preferentially distributed to dependent areas. Breathing oxygen seems to make little difference to distribution of blood flow in normal lungs. Apical underperfusion may increase when O_2 is breathed if hypoxic basal vasoconstriction is released.

c. Distribution of ventilation/perfusion ratios

There is a progressive fall in ventilation/perfusion ratios from apex to base in the normal upright lung of the order of 3 to 0.6. Lying down will decrease $\dot{V}/\dot{Q}$ ratio variance except in those in whom dependent airway closure occurs, increasing the proportion of lung with low $\dot{V}/\dot{Q}$ ratio. $\dot{V}/\dot{Q}$ ratio variance increases with increasing age. Breathing oxygen appears to have little effect on $\dot{V}/\dot{Q}$ ratio distribution in normal subjects.

d. Factors changing cardiac output and arterio-venous oxygen content difference

Cardiac output rises approximately 30% on lying down and since oxygen uptake is unaltered, $\Delta a\bar{v}C_{O_2}$ falls by 30%. The rise in cardiac output is due to increased venous return and stroke volume. These changes probably apply to acute changes and it seems that after 6 to 8 hours supine, cardiac output may return to near the original erect value.

Given a constant percentage venous admixture, the lower the mixed venous O_2 content the higher will be measured alveolar-to-arterial oxygen-tension difference. Thus $\Delta AaPO_2$ depends on $\Delta a\bar{v}C_{O_2}$. This emphasizes the importance of sampling mixed-venous blood to measure venous admixture when assessing lung function in people likely to have abnormal or changing $\Delta a\bar{v}C_{O_2}$.

If mixed-venous blood is not sampled and venous admixture is calculated from a measured $\Delta AaPO_2$ and an assumed $\Delta a\bar{v}C_{O_2}$ to assess postural changes one should assume a smaller $\Delta a\bar{v}C_{O_2}$ for the supine position than for the sitting position, otherwise supine admixture will be underestimated.

It is possible that $\dot{Q}_t$ falls a little with age and $\Delta a\bar{v}C_{O_2}$ rises. When healthy people change from breathing air to breathe oxygen, cardiac output and $\Delta a\bar{v}C_{O_2}$ probably do not change significantly although there is some evidence which suggests that cardiac output may fall.

e. Factors affecting $\Delta AaPO_2$, $\dot{Q}Va/\dot{Q}t$ and physiological dead space in health

Alveolar-to-arterial oxygen-tension difference is

produced by anatomical shunt, diffusion disequilibrium and ventilation/perfusion mismatching. Anatomical shunt is a small component of the total gradient and unlikely to change much with posture. It may increase a little with age and is unaffected by breathing oxygen. Diffusion disequilibrium is unlikely to be significant in normal people of any age breathing air or oxygen.

Ventilation/perfusion mismatching is the major component of the ΔAaP_{O_2}. Regions of lung with low $\dot{V}/\dot{Q}$ ratio will contribute to venous admixture. In the normal upright person there may be such regions at the lung base where perfusion is excessive in relation to ventilation. In the elderly (> 65 yr) these regions may be supplemented by alveoli subjected to airway closure and if some of these are totally unventilated they will contribute to intrapulmonary shunt. In subjects over 45 yr the fall in breathing level on lying down may mean that a greater number of dependent regions are subjected to airway closure and thus underventilated. Postural increase in venous admixture is greatest in the middle-aged. In young people pulmonary compliance is such that the change in breathing level on lying down may improve distribution of pulmonary ventilation, reduce $\dot{V}/\dot{Q}$ variance and reduce venous admixture.

ΔAaP_{O_2} and $\dot{Q}_{Va}/\dot{Q}_t$ increase with age. This is mainly due to increased $\dot{V}/\dot{Q}$ variance. An increase in anatomical shunt and $\Delta a\bar{v}C_{O_2}$ may contribute a little.

When oxygen is breathed the contribution to venous admixture of areas with low $\dot{V}/\dot{Q}$ ratio is abolished, since end-capillary blood is fully saturated even in poorly ventilated alveoli. However an addition to intrapulmonary shunt may arise

from alveoli with critically low $\dot{V}/\dot{Q}$ ratios, which collapse when their nitrogen is washed out and O_2 absorbed more quickly than it is delivered. Some of these alveoli remain closed even when O_2 is taken in deep breaths, and thus venous admixture measured under these conditions does not represent true anatomical shunt.

Measured venous admixture usually falls when O_2 is breathed but it is conceivable that it should rise above the air breathing level if areas of critically low $\dot{V}/\dot{Q}$ ratio are numerous.

ΔAaP_{O_2} rises with increasing alveolar oxygen tension (PAO_2). This is largely a function of the shape of the oxyhaemoglobin dissociation curve rather than an indication of deteriorating pulmonary function. The same percentage shunt produces a much larger ΔAaP_{O_2} when oxygen is breathed than when air is breathed. When end-pulmonary-capillary blood is fully saturated at a high P_{O_2}, the addition of under-saturated blood has a large effect on the arterial blood-gas tension. If there is a small fall in cardiac output on breathing O_2 this may produce a rise in ΔAaP_{O_2}.

The dependence of ΔAaP_{O_2} on PAO_2 and $\Delta a\bar{v}C_{O_2}$ indicates that $\dot{Q}_{Va}/\dot{Q}_t$ is a more specific index of pulmonary function because $\dot{V}_E$ and $\dot{Q}_t$ vary from one subject to another, and in the same subject from one occasion to another.

The more even distribution of pulmonary blood flow when supine leads to a fall in measured physiological dead space. Dead space increases with age and is an index of the increased $\dot{V}/\dot{Q}$ ratio variance. The effect of breathing oxygen on V_D is uncertain. There may be a small rise due to decreased apical perfusion.

In summary the alterations in gas exchange with a change

from the seated to supine position result from interaction of three factors, (1) the increase in $\dot{Q}_t$ with increased venous O_2 content; (2) the increased uniformity of perfusion distribution; (3) changes in $\dot{V}/\dot{Q}$ relationships which may be beneficial in young people and detrimental and associated with airway closure in the middle-aged and elderly.

Summary of the Relevant Literature

This will be divided into the following sections:

1. Mechanisms accounting for, and measurement of, the distribution of pulmonary ventilation ($\dot{V}$).
2. Effect of posture, age, and O_2 on the distribution of pulmonary ventilation.
3. Mechanisms accounting for, and measurement of the distribution of pulmonary perfusion ($\dot{Q}$).
4. Effect of posture, age and O_2 on the distribution of pulmonary perfusion.
5. Evidence for changes in $\Delta a\bar{v}C_{O_2}$ with posture and O_2 breathing.
6. Evidence for the influence of posture on ΔAaP_{O_2} and $\dot{Q}_{Va}/\dot{Q}_t$.
7. Evidence for the influence of age on ΔAaP_{O_2} and $\dot{Q}_{Va}/\dot{Q}_t$.
8. Evidence for the influence of breathing O_2 on ΔAaP_{O_2} and $\dot{Q}_{Va}/\dot{Q}_t$.
9. Alterations in physiological deadspace with posture, age and O_2 breathing.

1. Mechanisms accounting for, and measurement of, the distribution of pulmonary ventilation ($\dot{V}$).

Fowler (1952) laid the basis for the measurement and the physiological explanation of uneven distribution of ventilation.

Uneven distribution of $\dot{V}$ had been suggested by Krogh and Lindhard (1917). They found that after one inspiration of hydrogen (H_2) the succeeding expiration contained a greater concentration of H_2 in the alveolar gas expired early than in alveolar gas expired later in the same exhalation. They concluded that the distribution was not uniform i.e. the regions emptying late received less of the inspired H_2 than those emptying early.

Fowler further developed the analysis of single-breath tests. He measured expired N_2 concentration during the expiration following one inspiration of O_2 and noted the variable N_2 concentration of the alveolar plateau. He concluded that in healthy subjects the magnitude of the variation in plateau concentrations is so great that it must reasonably be attributed in major part to spatial and temporal unevenness of alveolar ventilation rather than to dead space contamination, respiratory quotient etc. Using multiple-breath tests Darling (1944) found that pulmonary N_2 clearance did not follow the course predicted for uniform ventilation.

Fowler (1952) discussed three theories to explain the sloping alveolar 'plateau':

(1) The stratification theory, which holds that there is a greater concentration of inspired gas in the proximal, alveolar spaces, ducts etc. than in the peripheral alveoli proper. Rauwerda (1946) calculated that any stratification which might be set up within alveolar spaces during inspiration of inert gas would be obliterated in so short a time that expired alveolar gas from a homogeneous compartment would show a uniform concentration of the reference gas. Diffusion times are very short in relation to the time of a single breath. It was thus felt that this did not explain the rising alveolar plateau for inert gases. The possibility that there was an intra-alveolar stratification of CO_2 and O_2 (though not explicitly stated) still existed.

(2) Regionally uneven ventilation i.e. different regional ventilations due to differences in distensibility. Fowler felt this had to be accepted, mainly by exclusion of other theories.

There was some radiological support from Dettrick and Tendeloo (cited by Rauwerda, 1946) who showed greater inspiratory brightening of the bases at fluoroscopy. Fowler concluded that in accepting this theory a major limitation had been the insufficient understanding of regional intrathoracic distribution of forces producing alveolar ventilation.

(3) Sequential ventilation i.e. preferential distribution of dead space to areas which fill first, and which by implication must empty last.

In summary, Fowler felt that uneven ventilation was probably due to variations in the proportional volume changes of various lung regions and/or preferential distribution of dead space gas.

Otis et al. (1956) suggested that uneven ventilation might involve temporal as well as spatial differences, and that these might arise in two ways: (1) all pulmonary pathways are similar mechanically but exposed to different driving pressures (I.P.P.); (2) pathways are not similar and behave asynchronously when exposed to the same driving force; if pulmonary pathways are thought of as consisting of a compliance and a resistance then different time-constants (R x C) would produce differences in distribution of $\dot{V}$ with change in respiratory frequency. Otis et al. found that distribution of pulmonary ventilation was uninfluenced by respiratory frequency (f) in healthy young adults but it was greatly altered by change in f in people with bronchospasm, indicating the presence of lung units with widely different time-constants.

Bouhuys and Lundin (1959) reviewed ideas on the

distribution of pulmonary ventilation and discussed theories of stratification and of series and parallel ventilation. They felt that Rauwerda's work indicated that stratification was likely to occur only at high respiratory frequency. Asynchronism and unequal regional volume expansion seemed to provide most of the explanation for the sloping single-breath curves. They also pointed out that unequal distribution of dead space gas, rather than accentuating ventilation differences, would tend to cancel the effect of different regional volume changes, because areas of high relative ventilation would inspire more dead space gas.

Bouhuys and Lundin (1959) described studies in which more uneven distribution of ventilation was shown with ageing; the effects of posture varied. In their conclusion they say "the hydrostatic pressure effects in pulmonary circulation appear to be compensated to some extent by changes in gas distribution but this compensation is insufficient to maintain uniform $\dot{V}/\dot{Q}$ ratios in the erect position".

Mead (1961) showed that the time-constants were very short in relation to the respiratory period and that in normal subjects distribution of $\dot{V}$ would depend largely on compliance. Also static (single breath) and dynamic (wash in) tests of distribution gave very similar results in healthy subjects, suggesting that regional airways resistance, likely to be more important in the dynamic situation, is of little importance in determining regional ventilation. Since distribution of inspired gas appeared independent of the breathing pattern it seemed that regional differences in ventilation must be due mainly to static factors e.g. intrapleural pressure.

In recent years knowledge of regional ventilatory function has advanced considerably as a result of studies using radioactive gases. The topographical nature of uneven ventilation has been quantified. Ball et al. (1962), West and Dollery (1960), West (1962), Milic-Emili et al. (1966), Kaneko et al. (1966), Bryan et al. (1964) and Dollfuss et al. (1967) have all reported studies using either radioactive carbon dioxide or xenon.

West and Dollery (using $C^{15}O_2$) and Bryan et al. (^{133}Xe) showed very similar patterns for the normal distribution of ventilation in relatively young subjects in the upright position. Making some assumptions about total ventilation and regional volumes they obtained the following results:

Ventilation ($l.min^{-1}$)

	Upper zone:	Mid zone:	Lower zone:
Bryan(^{133}Xe)	0.955	1.685	2.360
West and Dollery ($C^{15}O_2$)	0.99	1.78	2.31

The demonstration of a pleural pressure-gradient in upright man (Daly and Bondurant, 1963; Krueger et al., 1961; Milic-Emili et al., 1964) added much to the understanding of the mechanisms producing regional ventilatory differences.

In a series of ^{133}Xe studies Milic-Emili et al. (1966) and Anthonisen and Milic-Emili (1966) demonstrated regional differences in lung volumes, ventilation and perfusion. They showed how the ventilatory differences could be a consequence of regional differences in pleural pressure producing differences in effective regional compliance. These studies confirmed the work of West and Dollery (1960), West (1962), Ball et al. (1962)

and Bryan et al. (1964) on the distribution of ventilation, perfusion and $\dot{V}/\dot{Q}$ ratios in the upright position and added a convincing mechanical explanation. Other work indicated that the regional compliance changes did depend on pleural pressure and were not simply due to real lobar compliance differences (Clarke et al., 1969).

Radioactive isotope studies defined the normal distribution of ventilation upright, supine, changes with age and the importance of airway closure (Glaister, 1967; Jones, 1970; Holland et al., 1968; Anthonisen et al., 1969; and Kaneko et al., 1966).

To summarise: Krogh (1917) thought that the uneven alveolar plateau could be explained by uneven ventilation due to stratified inhomogeneity. This view was accepted until Rauwerda's calculations of the speed of gas mixing in the alveoli. The genesis of the rising alveolar plateau in the single breath N_2 test was then explained on the basis of different pathway time-constants and different regional ventilation, less well-ventilated areas contributing to the last part of expiration. Differential regional ventilation was accompanied, in this view, by sequential emptying. Mead's work posed some problems in explaining sequential emptying but was compatible with regional differences in distribution of inspirate.

When Milic-Emili et al. (1966) deduced that in the normal range of lung volume the compliance of different regions was not identical, and would explain ventilatory differences, the case in favour of regional inhomogeneity as a major factor in uneven alveolar ventilation seemed to have been made. However,

sequential emptying in the normal breathing range seemed unlikely from compliance studies and thus the slope of the alveolar plateau was not fully explained. The idea that, at the end of inspiration, there exists a concentration gradient from the bronchiolar opening to the alveolar wall was re-introduced by Cumming et al. (1967). They pointed out how Rauwerda's (1946) calculations depended on the assumed diffusion distance and it was felt he might have underestimated this. Cumming's group used an inspired mixture of two gases with very different diffusivity (Ne and SF_6). The ratio of the gases on expiration indicated that the heavy gas had remained in central parts of the respiratory tract and the light gas had moved more peripherally. This seems to confirm that stratified inhomogeneity exists.

Thus it seems that both parallel (regional) inhomogeneity and stratified inhomogeneity occur in the lung. With change in posture gravitational effects in regional ventilation are likely heavily to outweigh changes in stratified inhomogeneity.

2. Effect of posture, age and O_2 on distribution of $\dot{V}$.

Bryan et al. (1964) studied regional distribution of $\dot{V}$ and $\dot{Q}$ using ^{133}Xe in 31 normal subjects aged 22-44. They confirmed the finding of West and Dollery (1960) and Ball et al. (1962) with regard to the normal distribution in the upright posture. In 7 subjects they found the ventilation gradient from upper-zone to lower-zone demonstrable when erect was abolished when lying supine due to a significant increase in upper-zone ventilation and a fall in lower-zone ventilation. The gradient of perfusion was reversed as a result of a large rise in upper-zone blood flow.

Milic-Emili et al. (1966) reaffirmed the finding of normal distribution of $\dot{V}$ and $\dot{Q}$ and showed how gravity was important in both. They also showed how distribution of ventilation might be reversed by breathing at low lung volume. In 8 healthy young men distribution of ventilation and perfusion and $\dot{V}/\dot{Q}$ ratio was more uniform supine.

Glaister (1967) studied postural changes in pulmonary ventilation and perfusion using ^{133}Xe in 6 healthy men (31-48 yrs). With subjects seated erect the lung base was better ventilated than the apex in the ratio 1.5 to 1. Supine, this ratio became 0.9 to 1 and inverted head-down, 0.6 to 1. Corresponding base-to-apex ratios for blood flow were 3.0 to 1 erect, 1.3 to 1 supine and 0.7 to 1 head-down. This supported the theory that distribution of ventilation and perfusion was essentially gravity dependent.

Thus it seemed distribution of ventilation and perfusion at least in healthy people below 50 yr might be more evenly distributed in the supine position due to less gravitational differences from one region to another.

Holland et al. (1968) using ^{133}Xe studied ventilation and perfusion distribution in 6 normal men aged 65-75 yr. They showed that ventilation in the resting tidal range was not preferentially distributed to the lower zones as it was in young men. Blood flow, although increased to the upper zones, was still predominant in the lower zone. This distribution was similar to that seen in young adults when breathing near residual volume and was attributed to dependent airway closure. The mismatching of $\dot{V}/\dot{Q}$ thus produced might in part explain an increase in ΔAaP_{O2} with advancing age.

Thus, due to airway closure and its effects on distribution of ventilation, ageing and reduction in lung volume might have a detrimental effect on $\dot{V}/\dot{Q}$ matching. It was possible therefore that in the middle-aged and elderly, redistribution of ventilation on lying down (reduced expiratory reserve volume) could be disadvantageous.

Support for this idea came from many sources. Leblanc et al. (1970) measured closing volume using ^{133}Xe in 80 normal subjects aged 18-82 yr. Other lung volumes were measured sitting and supine. Closing volume increased linearly with age. On lying, CV changed little but ERV fell significantly. Seated, CV often exceeded ERV in subjects over 65 yr. While supine, ERV was markedly reduced and CV exceeded ERV at about 44 years. Above these two ages ventilation to dependent lung regions is likely to be reduced during normal tidal breathing. Thus in seated subjects older than 65 yr and in supine individuals over 44 yr there is often a significant impairment of ventilation distribution to dependent lung zones which probably causes impaired gas exchange.

Change to the supine position is thus likely to make the distribution of ventilation more even unless airway closure falls within the tidal breathing range.

Bryan et al. (1964) showed no significant difference in distribution of $\dot{V}$ in subjects who had duplicate studies breathing air and 100% O_2.

3. Mechanisms accounting for, and measurement of, the distribution of pulmonary perfusion

There is much evidence that gravitational forces

significantly influence the distribution of $\dot{Q}$ in the human lung. In 1887, Johannes Orth considered that the weight of the column of blood in the erect lungs might cause apical anaemia. More recently the use of radioactive gases has made possible the quantitative measurements of regional blood flow.

Mattson and Carlens (1955), and Carlens and Dahlstrom (1961) have shown greater O_2 uptake in dependent lobes of human lungs than could be explained by ventilatory differences alone. These authors concluded that at rest hydrostatic forces favour increased pulmonary circulation to dependent portions of the lungs at the expense of non-dependent segments.

West and Dollery (1960), counting the clearance rate of radioactive CO_2, reported that, in subjects standing at rest, there is a nearly linear reduction in CO_2 clearance from basal to apical lung segments without an equivalent change in ventilation.

Anthonisen and Milic-Emili (1966) used ^{133}Xe to measure regional pulmonary perfusion. They identified three zones of flow in the upright lung. Flow appeared to be absent in the upper 2.9 cm of the lung (zone 1), then increased rapidly down the lung (zone 2) until 15.20 cm from the top where the rate of increase in flow became less (zone 3). If the top of zone 2 was taken to represent mean pulmonary-artery pressure and the top of zone 3 to represent pulmonary venous pressure a close correspondence was found with directly measured vascular pressure.

4. Effect of posture, age and O_2 on distribution of pulmonary perfusion

In both the bronchospirometric and radioactive CO_2 studies the differential blood flow could be diminished by

exercise or changing to the supine position. Gravitational effects on regional pulmonary artery, alveolar and vein pressure seemed adequately to explain the observed changes in perfusion distribution.

Measurements of physiological dead space supported the concept of apical underperfusion when upright and more even distribution when supine. Riley et al. (1959) and Bryan et al. (1964) confirmed the radioactive CO_2 studies with regard to pulmonary perfusion distribution in the upright position. In 7 subjects aged 22-44 yr Bryan et al. showed that $\dot{V}/\dot{Q}$ distribution from apex to base when supine was more even than when standing though a perfusion gradient could be demonstrated from front to back. On lying down there was, per unit of volume, a 160% increase in perfusion of the upper zone and a 27% decrease in that of the lower zone.

Holland et al. (1968) used radioactive xenon to measure pulmonary $\dot{V}$ and $\dot{Q}$ distribution in 6 normal men aged 65-73 years, standing upright. Compared with six young subjects (Anthonisen and Milic-Emili, 1966) perfusion to the upper lung zones was increased in all the older subjects, although perfusion was still predominantly to the lower zone. Holland et al. assumed that the upper parts of the lung were better perfused in the older subjects because of a rise in pulmonary artery pressure, associated with increased vascular resistance in the lower zone.

Physiological dead space volume increases with age by an average of 9 ml for every 10 years of age (Harris et al., 1973). The increase is not in anatomical dead space (Hart et al., 1963). The effect of age on the CO_2 dead space is thus presumably due to

increasing $\dot{V}/\dot{Q}$ variance. Since it appears that ventilation and perfusion are redistributed in roughly the same direction with increasing age (both increasing apically) it is obviously the way in which changes are matched that is important in producing change in V_D and $\dot{Q}_{Va}/\dot{Q}_t$.

Increasing stratified inhomogeneity may contribute to increase in V_D with age. It is possible that the distance over which gas mixing occurs by diffusion may increase to important levels as in emphysema (Horsfield et al. 1966).

Larson and Severinghaus (1962) demonstrated an increase in arterial-to-alveolar CO_2 tension gradient ($\Delta aAPCO_2$), when healthy young adults breathed O_2. They suggest that this was the effect of O_2 "relaxing" the pulmonary vasculature leading to pooling of blood in dependent lobes and thus increasing V_D. Bryan et al. (1964) failed to show any redistribution of $\dot{V}$ or $\dot{Q}$ on 100% O_2 and suggested that part of the change in $\Delta aAPCO_2$ shown by Larson and Severinghaus (1962) is due to the effect of high O_2 tension on the transport of CO_2 (Haldane effect). Harris et al. (1973) showed an increase in V_D on breathing O_2 in only one of their age groups - women aged 40-50 years. Thus the effects of O_2 on distribution of $\dot{Q}$ are not definite and seem likely to be slight.

5. Evidence for changes in $\Delta a\bar{v}C_{O_2}$ with posture and O_2 breathing

Studies in which direct measurements of $\Delta a\bar{v}C_{O_2}$ in the sitting and supine positions are made show a mean fall, from sitting to lying, of 34% (Bevegard et al., 1960; Granath et al., 1964; Rapaport et al., 1966). On changing from sitting to lying ,

stroke volume increases (presumably due to increased venous return) and cardiac output increases despite a slight fall in heart rate. Oxygen uptake in unchanged.

Similar studies using dye-dilution (Chapman et al., 1960; Wang et al., 1960; Rigatto et al., 1968) yield a calculated mean fall in $\Delta a\bar{v}C_{O_2}$ of 29%. These changes with posture do not appear to be age-dependent.

The oxygen content of shunted blood is obviously important in determining the effect of shunt on ΔAaP_{O_2} as has been mentioned previously. The effect of the fall in $\Delta a\bar{v}C_{O_2}$ on lying would be to reduce ΔAaP_{O_2} slightly given a relatively constant venous admixture.

The above argument may apply only to acute changes of posture. Trimble (1972) measured $\dot{Q}_t$ in 7 men aged 19-24 yr by dye dilution at intervals during 48 hrs rest in bed. $\dot{Q}_t$ rose on first lying down but returned to the original value after 8-16 hr.

There is conflicting evidence in the literature concerning the effects of breathing O_2 on cardiac output and arterio-venous O_2 content difference. Whitehorn et al. (1946) measured cardiac output, from a ballistocardiogram, in 16 normal men aged 18-55 yr. Cardiac output was determined after the subjects had breathed room air for 15 min, 100% O_2 for 60 min and then room air again. The cardiac output was measured 6 times during the 60 min of O_2-breathing. Cardiac output fell during inhalation of O_2. The average decrease after 5 min of O_2-breathing was 13% and the value continued to decrease until an average of 19.4% was obtained at the end of 60 min. Cardiac output did not change significantly

from the first to the second air-breathing period. Dripps and Comroe (1947) described similar measurements. In 33 normal subjects $\dot{Q}_t$ was determined by ballistocardiography before and after 6-8 min breathing 100% O_2. Pulse rate and $\dot{Q}_t$ decreased 5.5 and 8.0% respectively when O_2 was breathed. Barratt-Boyes and Wood (1958) reported the effect of breathing 95% O_2, on $\dot{Q}_t$ and $\Delta a\bar{v}C_{O2}$, in 20 normal subjects. Mixed venous blood was sampled from a pulmonary-artery catheter and its O_2-content and the O_2-content of arterial blood were measured by the method of Van Slyke and Neill. Expired gas was collected in a Tissot spirometer and analysed in the Haldane apparatus. Measurements were made firstly while the subjects breathed air and then again after O_2 had been breathed for an average of 16 min. The average time separating the measurements of $\dot{Q}_t$ with the subjects breathing air and O_2 was 35 min. Arterio-venous O_2 content difference decreased by a mean value of 0.4 (SD 3.0) ml. l^{-1} when O_2 was breathed. The P value for the air/O_2 change of $\Delta a\bar{v}C_{O2}$ is given as < 0.6 which presumably means also > 0.5. There was no systematic change in $\dot{Q}_t$.

6. Evidence for the influence of posture on ΔAaP_{O2} and $\dot{Q}_{Va}/\dot{Q}_t$

Isotope studies have shown that $\dot{V}/\dot{Q}$ ratios decrease from apex to base in the normal upright lung (West and Dollery, 1960, 3.43 to .63; Bryan et al., 1964, 1.37 to .67). Thus apical regions contribute to measured physiological dead space and basal regions to venous admixture. $\dot{V}/\dot{Q}$ ratios are more evenly distributed on lying down (Bryan et al., 1964; Glaister, 1967; Kaneko et al., 1966) at least in young people, with consequent fall in ΔAaP_{O2} and $\dot{Q}_{Va}/\dot{Q}_t$ (Craig et al., 1971).

Malmberg (1966) measured ΔAaP_{O2} in 20 normal subjects and showed no difference between resting sitting and supine values. His subjects were aged from 19 to 58 yr. The postural changes were not classified by age groups. Riley et al. (1959) measured ΔAaP_{O2} during a study of postural effects on V_D; mean values for 7 subjects aged from 21 to 31 yr were 10.3 mm Hg standing and 6.4 supine. Cole and Bishop (1963) measured ΔAaP_{O2} in eight normal men and eight women. The subjects fell into two age groups, 20 to 29 yr and 50 to 59 yr, and each subject was studied sitting and supine. Sitting, ΔAaP_{O2} was greater in the older groups than the younger (14.9 mm Hg and 7.9 respectively). Mean ΔAaP_{O2} supine was 9.2 mm Hg in the young group and in the older group 14.2 mm Hg. They concluded posture had little effect on ΔAaP_{O2}.

The study of Holland et al. (1968) on $\dot{V}/\dot{Q}$ in old men (65-75 yr) using ^{133}Xe was the first demonstration that during normal tidal breathing the usual preferential distribution of $\dot{V}$ to the lung bases is reversed with advancing age. Holland et al. speculated on dependent airway closure as a cause of low $\dot{V}/\dot{Q}$ ratios. They suggest that the resulting rise in $\dot{Q}_{Va}/\dot{Q}_t$ might explain the bigger ΔAaP_{O2} and the lower arterial PO_2 in the elderly.

The concept of 'reversed mismatching' of ventilation due to dependent airway closure within the normal breathing range was further elucidated by Leblanc et al. (1970). They showed that CV is likely to exceed ERV in those over 65 years when upright, and in those over 44 years when supine.

The implications that this would increase ΔAaP_{O2} and $\dot{Q}_{Va}$, and lower arterial PO_2, in the elderly upright and middle-aged supine subject was later confirmed by Craig et al. (1971).

Their study showed that the individual postural changes in gas exchange in a group of 22 normal subjects aged 21-78 yr could be logically explained by the individual postural changes in CV and ERV. Postural changes in ΔAaP_{O_2} were not found when the subjects were grouped according to age, weight or smoking history, and the mean ΔAaP_{O_2} of the group as a whole was not different sitting or lying. These results indicated the importance of airway closure as a mechanism capable of impairing gas exchange. The poor correlation of postural increase in $\dot{Q}_{Va}/\dot{Q}_t$ with age indicated that factors such as weight (reduced ERV) and smoking (increased CV) might be more important in determining supine gas exchange. This might explain why there is little difference in the ΔAaP_{O2} postural changes between Cole and Bishop's (1963) old and young groups; they might have had unusual CV/ERV relationships.

Indirect evidence for postural deterioration in $\dot{V}/\dot{Q}$ matching and blood-gas exchange comes from several studies. Ward et al. (1968) and Hamosh and DaSilva (1973) described postural arterial hypoxemia sufficient to produce polycythaemia in several patients. The patients of Ward et al. were mildly obese and the authors suggested that abnormal $\dot{V}/\dot{Q}$ ratios are produced when fat people lie down. Hamosh and DaSilva demonstrated that when supine, closing volume exceeded ERV in their patients and that dependent zonal airway closure was probably the cause of their arterial hypoxaemia. The haematocrit of one of their subjects fell after being propped up during sleep for 3 months.

Strieder et al. (1969) showed postural hypoxaemia in a group of asymptomatic smokers. Ten non-smokers (whose mean

age was 35 yr) had a mean ΔAaP_{O_2} of 13 mm Hg erect and 12 mm Hg supine. Thirteen smokers (mean age 36 yr) had ΔAaP_{O_2} of 18 mm Hg erect and 23 mm Hg supine. The deterioration in smokers on lying may be due to airway closure occurring within the breathing range.

Ward et al. (1966) measured arterial P_{O_2} in 50 patients aged 60 yr or over sitting, and in another 50 supine. None had demonstrable cardiac or pulmonary disease. Mean Pa_{O_2} of the patients sitting was 85 mm Hg (SD ± 12) supine 77 mm Hg (SD ± 11, $P < .005$).

Thus it seems that the changes from the erect to the supine position improves $\dot{V}/\dot{Q}$ matching in the young, but after middle age, with obesity or smoking, $\dot{V}/\dot{Q}$ redistribution may lead to increased dependent-zone underventilation and increase in venous admixture.

7. Evidence for the influence of age on ΔAaP_{O_2} and $\dot{Q}_{Va}/\dot{Q}_t$

Holland et al. (1968), using ^{133}Xe, showed that the normal erect distribution of ventilation seen in the young is reversed at 65 yr and over, so that regions which are the better perfused become less well ventilated. There is also evidence that blood-gas exchange deteriorates with age. Raine and Bishop (1963) measured dead space and ΔAaP_{O_2} in 70 normal subjects aged 17-66 yr. The mean ΔAaP_{O_2}, while sitting, in subjects less than 40 yr was 5.9 mm Hg, while for those over 40 yr it was 16.7 mm Hg. Raine and Bishop dismissed diffusion defects as the cause of the increase. They assumed that ΔAaP_{O_2} measured breathing O_2 indicated the contribution of true shunt; they

calculated this would only contribute 2-3 mm Hg breathing air. Raine and Bishop concluded that the rising ΔAaP_{O_2} with age was due to increasing unevenness in the distribution of $\dot{V}/\dot{Q}$ ratios in the lung.

Cole and Bishop (1963) investigated the effect of varying inspired O_2 tension on ΔAaP_{O_2}. Their 16 subjects were selected equally from the age groups 20-29 yr and 50-59 yr. ΔAaP_{O_2} was again consistently higher at all levels of PAO_2 in the older group.

Harris et al. (1974) measured ΔAaP_{O_2} in 48 healthy subjects while breathing a range of O_2 concentrations. The gradient increased with age. When breathing air the distribution seemed homoscedastic and the regression equation was ΔAaP_{O2} = 0.264 x age - 0.43 with r = 0.5569. Breathing O_2 the increase with age appeared heteroscedastic. Harris et al. assumed that breathing O_2 in deep breaths gave a gradient which was due to anatomical shunt (they later showed (1976) that this was incorrect). On this assumption they showed that the major influence increasing ΔAaP_{O_2} with age was anatomical shunt, since allowing for it largely abolished the differences in gradient between age groups. The gradient which was not due to anatomical shunt when breathing air remained higher in those over 60 yr than in the younger subjects and these workers suggested that this could be due to cyclical airway closure in the older group.

Harris et al. (1976) showed that the lowest values for $\dot{Q}_{Va}/\dot{Q}_t$ on oxygen are found during exercise and used this and other evidence to suggest that $\dot{Q}_{Va}/\dot{Q}_t$ measured while breathing O_2 in deep breaths at rest does not represent anatomical shunt. It

seems likely that while breathing O_2 some alveoli with critically low $\dot{V}/\dot{Q}$ close (Wagner et al., 1974) and that these are not opened even by deep breathing. Thus the finding (Harris et al., 1974) of increasing ΔAaP_{O2} with age is quite compatible with increasing $\dot{V}/\dot{Q}$ variance and especially with increasing areas of critically low $\dot{V}/\dot{Q}$ which close when O_2 is breathed rather than due merely to increase in $\dot{Q}s$ and cyclical airway closure in those over 60 yr.

8. Evidence for the influence of breathing O_2 on ΔAaP_{O2} and $\dot{Q}_{Va}/\dot{Q}_t$

Pulmonary artery pressure falls when pure O_2 is breathed in patients with chronic bronchitis and emphysema (Fishman et al., 1952). This has been attributed to release of vasoconstriction in hypoxic areas of lung. Whether perfusion is significantly redistributed in normal people when they breathe O_2 is uncertain. Bryan's (1964) study suggests that at least in his youngish group breathing O_2 makes little difference to the $\dot{V}/\dot{Q}$ matching.

Ventilation is probably little affected in young people by breathing O_2 but Wagner et al. (1974) have shown that areas with critically low $\dot{V}/\dot{Q}$ may suffer alveolar collapse. In health, this might not make much difference to overall $\dot{V}/\dot{Q}$ variance. Presumably in people with extensive regions of low $\dot{V}/\dot{Q}$ pulmonary perfusion may be altered by breathing O_2. Basal areas hypoxic when air was breathed, might steel perfusion and increase apical underperfusion if breathing O_2 increased their alveolar PO_2.

$\Delta AaPO_2$ is highly sensitive to change in alveolar PO_2. Cole and Bishop (1967) measured ΔAaP_{O2} at mean PAO_2 of 100, 174,

293, 392, 526 and 651 mm Hg. The corresponding mean values for $\Delta AaPO_2$ in 6 young men were 9.6, 20.0, 20.2, 15.2, 22.0 and 10.3 and in 6 older men 17.1, 39.3, 39.3, 40.2, 39.8 and 21.8 mm Hg. Cole and Bishop pointed out that the rise in $\Delta AaPO_2$ above PAO_2 of 170 mm Hg is a feature of the effect of venous admixture on fully saturated end-capillary blood, and of the slope of the oxyhaemoglobin dissociation curve, rather than an indication of alteration in pulmonary blood-gas exchange. To account for the fall in $\Delta AaPO_2$ between PAO_2 513 and 650 they concluded some sort of $\dot{V}/\dot{Q}$ variance must be present at tensions up to 513 mm Hg that was abolished breathing pure O_2. According to the theoretical model of Farhi and Rahn (1955) no such fall in gradient should occur. Harris et al. (1974) showed that $\Delta AaPO_2$ increased with inspired O_2 concentration up to 60%. Above 60% there was no significant further change in gradient. In 16 subjects in each of the age groups 20-30 yr, 40-50 yr and 60 yr and over, at F_{IO_2} of 14, 21, 40, 60 and 100%, mean $\Delta AaPO_2$'s were:

20-30 yr	2.2	6.4	25.9	33.1	33.0
40-50 yr	2.9	10.5	38.4	51.4	57.0
60 + yr	5.5	17.4	56.0	76.4	67.3

Harris discusses the possible reasons for the difference in gradient on 'pure' O_2 between Cole and Bishop's (1967) results and his study. He suggests that their estimates of $F_{E_{N_2}}$ of up to 2%, which were based on analysis of $F_{E_{O_2}}$ and $F_{E_{CO_2}}$ by the Scholander method, may be excessive for tissue nitrogen washout and may have led to their underestimating PAO_2. The Scholander method underestimates F_{O_2} increasingly at high O_2 concentrations. Cole and Bishop used the Scholander method in both their 1963 and 1967 studies.

Harris et al. (1974) assumed a $\Delta a\bar{v}C_{O_2}$ of 50 ml. l^{-1} for all their subjects at all values of $F_{I_{O_2}}$ and calculated $\dot{Q}_{Va}/\dot{Q}_t$. At $F_{I_{O_2}}$ of 21, 40, 60, 100% results were as follows:

20-30 yr	1.5,	2.0,	2.2,	2.0
40-50 yr	2.8,	2.9,	3.2,	3.4
60 + yr	5.3,	4.5,	4.6,	4.0

This shows how $\Delta AaPO_2$ is influenced by alveolar PO_2, whereas calculated venous admixture is relatively unchanged. If venous admixture breathing O_2 is greater than on air, this suggests the presence of alveoli with critically low $\dot{V}/\dot{Q}$ which collapse when O_2 is breathed; alternatively the assumption of $\Delta a\bar{v}C_{O_2}$ may be incorrect.

Harris et al. (1974) do not discuss nor allow for the possible effect of O_2 on cardiac output and $\Delta a\bar{v}C_{O_2}$. The study of Barratt-Boyes and Wood (1958) indicates that there may be very little change in $\Delta a\bar{v}C_{O_2}$, when O_2 is breathed. Cole and Bishop (1963, 1967) calculated that a rise in $\Delta a\bar{v}C_{O_2}$ would only have very small effect on $\Delta AaPO_2$. With admixtures in the 2-4% range this is likely to be true. With bigger admixtures the effect of changing $\Delta a\bar{v}C_{O_2}$ on measured $\Delta AaPO_2$ might be highly significant. This makes direct measurement of $\Delta a\bar{v}C_{O_2}$ essential when there is any reason to suppose that cardiac output may not be normal.

The possible contribution of altered $\Delta a\bar{v}C_{O_2}$ to measured $\Delta AaPO_2$ breathing O_2 in normal subjects can be calculated.

Assume PAO_2 = 666 mm Hg, $C\acute{c}O_2$ = 220 ml. l^{-1} and $C\bar{v}O_2$ = 170 ml. l^{-1}; therefore with 2% admixture CaO_2 = 219 ml. l^{-1} PaO_2 = 630 mm Hg and $\Delta AaPO_2$ = 33 mm Hg.

If cardiac output fell significantly breathing O_2 and $C\bar{v}O_2$ fell to

140 ml. l^{-1} (a much bigger change than is likely) then with a 2% admixture CaO_2 = 218.4 ml. l^{-1} PaO_2 = 613 mm Hg and $\Delta AaPO_2$ = 53 mm Hg. Thus 20 mm Hg of the gradient is due to the change in cardiac output. A change in $\Delta a\bar{v}C_{O_2}$ might thus contribute something to the rise in $\Delta AaPO_2$ when O_2 is breathed. This is unlikely to be significant in normal subjects, but might be in people with big venous admixtures.

9. Alterations in physiological dead space with posture, age and O_2 breathing

Many of these have been discussed already under different headings.

The more even distribution of pulmonary blood flow on lying down reduces the high $\dot{V}/\dot{Q}$ areas at the lung apex (Bryan et al., 1964; Glaister, 1967; Kaneko et al., 1966) with subsequent reduction in measured physiological dead space (Raine & Bishop, 1963; Riley et al., 1959; Larson & Severinghaus, 1962). Riley et al. (1959) found V_D was on average 83 ml higher standing upright than in the supine position in 7 normal men. He estimated that, in effect, one-seventh of the total number of alveoli became non-perfused on changing from supine to erect posture. He thought the changes were too big to be due to change in anatomical dead space. Tidal volume and frequency happened to be nearly the same in both positions.

Raine and Bishop (1963) measured V_D sitting and supine in 70 normal subjects aged 17-66 yr. Supine, the mean V_D/V_T ratio was 16.5% in subjects younger than 40 yr and 23.7% in those over 40 yr. In the sitting position corresponding values were 23.8% and 26% but sitting and lying measurements were not made in the same subjects.

Larson and Severinghaus (1962) examined postural effects on anatomical (ADS) and physiological (PDS) dead space and $\Delta aAPCO_2$ in 11 healthy adults. They showed that in moving from the supine to the sitting position ADS and PDS increased by corresponding amounts (42 and 37 ml respectively) with no significant increase in alveolar dead space. Their measurement of ADS from a Fowler-type single-breath technique, using CO_2 as the indicator gas, may be suspect and might account for the difference between their finding and Riley's. Riley's upright subjects were standing and Larson's sitting, and there was probably a greater change in cardiac output in Riley's subjects.

Measurement of changes in ADS with posture have given variable results. Fowler (1950) found a mean increase of 46 ml on moving from the supine to the sitting position but others (Riley et al., 1959; Wilson et al., 1956) subsequently noted much smaller differences. The fall in ADS which occurs with a change from the sitting position to lying is probably related to the fall in FRC. Hart, Orzalesi and Cook (1963) measured ADS, in 73 normal subjects aged 4-42 yr, by the single breath N_2-washout method of Fowler (1948). ADS was closely correlated with height and FRC. The latter relationship was described by the equation:

$$ADS = 38.55 \times FRC + 40.76.$$

Whitfield et al. (1950) measured the fall in FRC which followed change from sitting to lying. These authors measured FRC by the closed circuit hydrogen dilution method in 56 healthy subjects. Mean FRC sitting was 2.933 ml and lying 2.288 ml. Using the equation of Hart et al. (1963) a fall in ADS of 25 ml would be expected in a subject with this FRC following a change from sitting to lying.

This is considerably less than the changes in physiological dead space measured by Riley et al. (1959). Evidence from bronchospirometric and isotope studies and the known inaccuracies of ADS measurement (Norris, 1967) make it highly likely that alveolar dead space does fall on lying down. Posture might have less effect on V_D in the elderly (Raine & Bishop, 1963) due to higher P.A. pressure and apical flow (Holland et al., 1968). Larson and Severinghaus (1962) studied the effect of O_2 breathing on dead space. Alveolar V_D was minimally increased both sitting and supine and $\Delta aAPCO_2$ more than doubled. They suggested that high alveolar PO_2 may have a relaxing influence on the pulmonary vascular bed diverting the major volume of pulmonary flow through dependent portions of the lung leaving non dependent segments relatively underperfused. Bryan et al. (1964) suggested that this change in CO_2 gradient was likely to be due to the effect of O_2 on CO_2 transport. Also the difficulty of measuring $PACO_2$ accurately makes such conclusions speculative. As mentioned before it seems unlikely that breathing O_2 would greatly affect distribution of pulmonary perfusion in lungs with few hypoxic areas. However, O_2-breathing might affect measured V_D by reducing cardiac output and thus increasing underperfusion in non-dependent areas.

Harris et al. (1973) showed that physiological dead space increased with age. These workers also pointed out the difficulty in comparing V_D measurements made under different circumstances and in predicting normal values, since V_D is sensitive to changes in V_T, f, inspiratory lung volume and body size. The V_D/V_T ratio overcomes this problem to some extent, allowing roughly for differences in end-inspiratory lung volume and body size. Harris

et al. (1973) found the best prediction could be made by multiple regression of V_D on age, height, tidal volume and the reciprocal of respiratory frequency, and the effects of these should all logically be considered in comparing one V_D measurement with another.

Conclusions from the review of the literature

Published work in which $\Delta AaPO_2$ has been measured, supine breathing air and O_2, in normal subjects. Means, with S.D. in brackets.

Reference	Number of subjects	Age (yr)	$\Delta AaPO_2$ (mm Hg) supine	
			Air	Oxygen
Riley et al. (1959)	7	21-34	7.4 (2.5)	
Raine & Bishop (1963)	14	< 40	6.4 (5.6)	
	7	> 39	15.6 (6.8)	
Cole & Bishop (1963)	8	20-29	9.2 (4.7)	4.1 (11.0)
	8	50-59	14.2 (7.3)	20.8 (19.1)
Malmberg (1966)	18	19-58	10.5 (9.3)	
Cardus (1967)	7	21-25	9.0 (6.7)	
Trimble et al. (1972)	7	19-24	9.9 (6.5)	

The table above summarises the published normal data on supine gas exchange. None of these studies is satisfactory to help in the assessment of the patients going forward for coronary vein-graft operation. Only the study of Cole and Bishop (1963) meets the requirements with regard to evaluation breathing both air and oxygen and as discussed previously there are some reservations about the accuracy of their measurements during O_2-breathing. It was, therefore, decided to proceed with a study to try to set normal values for pulmonary blood-gas exchange, supine, breathing air and oxygen.

Materials and Methods

Subjects

Details of the subjects are shown in Table 1, grouped according to age. None was a hospital patient. The purpose of the study and procedure were explained to each volunteer. All had had normal roentgenograms of the chest within one year of the study, and in all subjects of Group C a 12-lead electro-cardiogram was recorded and was normal. All completed an abbreviated respiratory questionnaire with a normal result.

Procedure

Each subject attended the laboratory on two occasions separated by less than 1 week. On the first day a history was taken and a physical examination made. Slow and forced spirograms were made and specific airways resistance (SRaw), functional residual capacity and CV were measured in the sitting position. A second spirogram was made with the subject supine, and expiratory reserve volume was measured. At the 2nd attendance, V_D, $\Delta AaPO_2$ and $\dot{Q}_{Va}/\dot{Q}_t$ were measured sitting and lying, and breathing air and oxygen, by techniques described below and previously described by Harris et al. (1973, 1974, and 1976). The order of sitting-lying and air-O_2 sequences were varied according to 4 X 4 Latin squares. At the end of each O_2-breathing period the subject was asked to take deep breaths (from FRC to TLC) of O_2 for 2 min, reducing respiratory frequency (f) as necessary to avoid discomfort.

SRaw and FRC were measured in an Ohio Instruments body-plethysmograph (Dubois et al., 1956). Closing volume was measured by a single-breath N_2 method (National Heart and Lung Institute, 1973)

using a 500-ml bolus of air followed by O_2 from the wall supply (mean 99.73% by volume), a bag-in-box, a Med-Sci model 565 rolling-seal spirometer, and a Hewlett-Packard model 47302A N_2-analyzer. During the vital-capacity (VC) manoeuvre inspiratory and expiratory flow was kept at or below 0.5 $1.s^{-1}$. A N_2-concentration/volume plot was displayed via a PDP8E computer on a storage oscilloscope; specific points on this plot were selected visually and marked on the trace by a manually-operated, bright-spot cursor, and the co-ordinates of these points fed back into the computer for analysis. CV was identified as the point judged by an experienced observer to be the first at which the curve departs from the alveolar plateau (phase III). Curves were rejected if (a) inspired VC differed by more than 5% from expired VC, or (b) either VC differed by more than 10% from the previous spirographic measurement. All subjects produced 2, and most 3, satisfactory curves.

In the gas-exchange studies humidified air or oxygen was delivered to the inspiratory port of a Lloyd breathing-valve by a modification of the method of Cunningham et al. (1957). Expired gas passed through an 8-litre mixing chamber and thence via a pneumotachygraph head to a Parkinson-Cowan CD4 dry gas-meter. Signals for each half-litre and each breath were recorded on a Mingograf 800 recorder. Expired gas was sampled from a point distal to the mixing chamber and analyzed for CO_2 by a URAS-M infra-red analyzer, for O_2 by a Servomex OA150 paramagnetic analyzer, and for N_2 by a Med Sci model 505 nitrogen meter. The outputs of the CO_2 and O_2 analyzers were read from a digital voltmeter (Dana 4430); this procedure has been previously validated (Harris, 1973; Ellis and Nunn, 1968). 95%-confidence limits for a single estimate of F_{CO_2}

were ±0.023, and for F_{O_2} ±0.036 volumes per cent. The nitrogen meter was accurate to within 0.1 per cent in the range 0-4 per cent by volume. Inspired gas was sampled from a point 2 cm upstream from the inspiratory flap of the Lloyd valve; the breath-by-breath record of CO_2-concentration at this point provided a check on the competence of the flap, an important source of error in measurement of V_D.

No measurements were made for the first 10 min on either air or O_2. During the next 5 min ventilation ($\dot{V}_E$) and expired O_2 and CO_2 concentrations ($F_{E_{O_2}}$, $F_{E_{CO_2}}$) were read every minute and only if no systematic change occurred in any of these were the definitive measurements started. Readings were then taken every min for 6 min of $F_{E_{O_2}}$, $F_{E_{CO_2}}$, $\dot{V}_E$ and respiratory frequence (f) in the steady state of air- and O_2-breathing. During the 2nd and 5th min, 5-ml samples of arterial blood were drawn evenly from a radial-artery catheter into heparinized glass syringes. Inspired O_2 and CO_2 concentration (F_{IO_2}, $F_{I_{CO_2}}$) were measured immediately before and after the 6-min period. Expired N_2 concentration ($F_{E_{N_2}}$) was continuously recorded during O_2-breathing to ensure that $F_{E_{N_2}}$ was less than 1% during the sampling period.

Blood-gas analysis

Within 3 min of sampling, blood was introduced into the cuvette of an O_2 electrode (Radiometer E 5046) set at the subject's oral temperature, calibrated immediately beforehand with humidified gases analyzed by the Haldane-Lloyd method; 8% CO_2 in O_2-free N_2 was used for zero PO_2 and 3% CO_2 in either air or O_2 for high PO_2, depending on the expected blood PO_2. The blood PO_2 was read by the

procedure of Severinghaus and Bradley (1971) and the reading was obtained no more than 6 min after sampling. Two O_2 electrodes were set up to avoid delay in analyzing duplicate samples. Immediately after filling the O_2 electrode, the syringe was immersed in ice-and-water. Within 10 min a CO_2 electrode (Radiometer E5036) at the subject's oral temperature was filled from it. PO_2 and PCO_2 were read on either a Radiometer PHM 72 or Beckman 160 electrometer. At the same time pH was read at the subject's temperature from the iced sample (Radiometer electrode E 5021 and PHM 72).

Corrections were applied to the PO_2 readings as follows. First the gas/blood calibration ratio, determined after each experiment by rotating-flask tonometry was applied. Next, dilution of the sample by heparin in the syringe (dead space 0.3 ml with steel mixing-washer) was corrected for (Lübbers, 1966). Finally the resulting PO_2 was corrected for the time-interval between sampling and reading (measured by stopwatch) and also for any small difference in temperature between the electrode and the subject (never > 0.2°C) by the procedure of Kelman and Nunn (1966). By this two-electrode method differences between duplicate estimations of PO_2 on ten samples of blood showed standard deviations (SD) of 2.9 mm Hg at a PO_2 of 100 mm Hg and 33.3 mm Hg at a PO_2 of 500-680 mm Hg. The readings of blood PCO_2 and pH were corrected if necessary to the subject's oral temperature (Kelman, 1966). No correction for elapsed time was made. For a single estimate of PCO_2, 95%-confidence limits lay between ±0.41 mm Hg.

Calculations were made from each half of the 6-min sampling period, using average values of $F_{E_{CO_2}}$ and $F_{E_{O2}}$ and the O_2 and CO_2 tensions and pH of the appropriate blood sample. A further sample of arterial blood was taken during the 2nd min of each 2-min deep-

breathing period on O_2, while the record of $F_{E_{N_2}}$ was closely watched to make sure that room air had not leaked around the mouthpiece.

Calculations

V_D was calculated from the Enghoff modification of the Bohr equation

$$V_D = V_T \ (PaCO_2 - P_{E_{CO_2}})/PaCO_2$$

The valve dead space was 40 ml and this was subtracted from the calculated dead space.

Alveolar PO_2 was derived via the alveolar-gas equation:

$$PAO_2 = P_{I_{O_2}} - PaCO_2 \ \left[F_{I_{O_2}} + (1 - F_{I_{O_2}})/R \right]$$

breathing air, and from the following modified equation (Harris et al., 1974) breathing oxygen:

$$PAO_2 = 0.9973 \ (P_B - 47) - PaCO_2$$

Venous admixture was calculated from the following modification of the shunt equation:

$$\dot{Q}_{Va}/\dot{Q}_t = (C\acute{c}O_2 - CaO_2)/ \left[(C\acute{c}O_2 - CaO_2) + (CaO_2 - C\bar{v}O_2) \right]$$

where end-pulmonary-capillary and arterial O_2 contents ($C\acute{c}O_2$, CaO_2) were calculated from PAO_2 and PaO_2, with $PaCO_2$, haemoglobin concentration and arterial pH via Kelman's (1966) subroutine. Arteriovenous O_2-content difference was assumed to be 50 ml. l^{-1} in the sitting position and 35 ml. l^{-1} in the supine position and to be the same for air and for O_2 breathing periods.

Statistical analyses (t-tests and regressions) were made according to standard procedures (Davies, 1961). There was no systematic change in any variable from one member of a duplicate to the other (i.e. individual 3-min values in each 6-min period) and all data are presented as means of duplicates.

Results

Lung volumes and airway resistance

Table 1 shows that FRC, VC, TLC and SRaw were within normal limits in all subjects.

Closing volume

Seventy-five VC curves were recorded. Of these, 8 did not meet the stated criteria and were rejected. Individual values for CV and ERV are shown in table 1. CV was measured sitting and has been assumed to be the same in the supine position (see Discussion). ERV was measured sitting and supine and the value of CV-ERV is used as an index of the relationship between CV and the tidal breathing level in each position. In all but one subject CV was normal for age (Buist and Ross, 1973); subject 11 had a CV/VC of 23%, just above the upper 95%-confidence limit for healthy non-smokers.

In table 1 subjects have been grouped according to age and have been assigned a group according to the relation of CV to breathing level in the two positions. Closing volume was less than ERV in all subjects in group A, in 1 of group B and in 5 of group C in both the lying and sitting positions (CV-ERV negative in both positions, group 1). In two subjects of group C and 6 of group B, CV exceeded the expiratory level in the supine but not the sitting position (CV-ERV negative sitting, positive supine, group 2). In one subject in group B and one of group C, CV exceeded ERV both sitting and supine (CV-ERV positive both sitting and supine, group 3).

Table 1. Characteristics and basic pulmonary data of subjects.

Subject	Age	Sex	Weight (kg)	Height (cm)	Cigarettes per day	Sitting VC(1)	FRC(1)	TLC(1)	S_{Raw} ($cm.H_2O.s$)	CV(1)	ERV(1)	CV-ERV(1)	Lying ERV(1)	Lying CV-ERV(1)	CV/ERV GROUP
GROUP A															
1. H.R.	29	M	74.0	175.0	0	5.15	3.38	6.62	7.7	0.555	1.910	-1.355	1.540	-0.985	1
2. T.W.	25	M	70.4	179.0	10	6.03	3.35	7.34	7.0	0.296	2.050	-1.754	1.300	-1.004	1
3. B.McL.	23	M	82.6	173.0	0	5.45	2.84	6.84	6.2	0.586	1.450	-0.864	0.840	-0.254	1
4. B.B.	27	M	67.0	161.5	0	3.53	1.72	4.32	5.8	0.388	0.935	-0.547	0.623	-0.235	1
5. H.W.	29	F	57.0	172.0	0	4.49	4.04	6.26	10.1	0.393	2.270	-1.877	1.290	-0.897	1
6. C.B.	23	F	53.8	158.0	10	3.16	2.52	4.37	6.7	0.260	1.390	-1.130	0.580	-0.320	1
7. R.K.	25	F	58.2	172.5	0	3.90	2.77	5.09	5.8	0.178	1.580	-1.402	0.770	-0.592	1
8. M.C.	25	F	61.5	166.0	0	4.02	2.73	5.40	8.3	0.289	1.290	-1.000	0.860	-0.571	1
MEAN	25.75		65.56	169.6		4.466	2.919	5.780	7.20	0.368	1.610	-1.241	0.976	-0.608	
SD	2.375		9.778	7.135		0.999	0.688	1.149	1.47	0.143	0.440	0.447	0.354	0.323	
GROUP B															
9. R.L.	45	M	79.0	169.0	0	4.81	3.14	6.59	7.3	0.907	1.440	-0.533	0.800	+0.107	2
10. K.H.	44	M	91.0	175.0	0	4.73	2.95	7.12	6.2	0.908	0.560	+0.348	0.285	+0.623	3
11. P.M.	46	M	80.4	170.5	1	4.97	2.73	6.48	6.5	1.145	1.220	-0.075	0.640	+0.505	2
12. C.C.	47	M	86.2	181.2	0	5.34	2.71	6.99	6.5	0.922	1.060	-0.138	0.420	+0.502	2
13. B.M.	40	F	75.2	163.0	0	3.47	2.43	5.05	7.5	0.558	0.850	-0.292	0.360	+0.198	2
14. M.C.	46	F	83.3	164.0	0	3.43	2.48	4.91	5.6	0.521	1.000	-0.479	0.330	+0.191	2
15. M.W.	40	F	62.5	166.3	0	4.56	2.63	5.87	4.9	0.818	1.490	-0.672	0.700	+0.118	2
16. B.L.	48	F	62.8	171.0	0	4.32	3.19	6.55	10.6	0.551	1.790	-1.239	0.960	-0.409	1
MEAN	44.5		77.55	170.0		4.454	2.783	6.195	6.89	0.791	1.176	-0.385	0.562	+0.229	
SD	3.024		10.34	5.993		0.687	0.285	0.838	1.72	0.225	0.392	0.470	0.248	0.326	
GROUP C															
17. P.L.	72	M	79.0	178.0	20	3.97	3.61	6.74	5.8	0.763	0.840	-0.077	0.105	+0.658	2
18. M.S.	61	M	71.5	184.7	0	6.40	5.05	9.15	4.8	1.286	2.300	-1.014	1.350	-0.064	1
19. R.H.	61	M	83.5	176.0	0	4.48	3.44	6.88	9.3	0.234	1.040	-0.806	0.720	-0.486	1
20. P.P.	61	M	88.4	182.0	0	5.06	4.10	7.64	8.7	1.042	1.520	-0.478	1.300	-0.258	1
21. E.S.	70	F	39.2	145.0	0	2.45	2.67	4.18	5.0	0.510	0.940	-0.430	0.330	+0.180	2
22. C.V.	62	F	60.1	146.0	0	2.34	2.10	3.99	9.0	0.238	0.450	-0.212	0.270	-0.032	1
23. M.C.	65	F	70.5	157.0	0	2.83	3.00	5.13	10.0	0.439	0.550	-0.111	0.480	-0.041	1
24. E.S.	65	F	67.6	157.0	0	2.25	2.13	4.05	2.9	0.612	0.220	+0.392	0.160	+0.452	3
MEAN	64.63		69.975	165.7		3.723	3.263	5.970	6.94	0.641	0.983	-0.342	0.589	+0.051	
SD	4.307		15.38	16.27		1.516	1.007	1.921	2.63	0.374	0.666	0.443	0.493	0.370	

Groups 1-3 are based on CV and ERV: 1, CV less than ERV sitting and supine; 2, CV less than ERV sitting but greater supine; 3, CV greater than ERV sitting and supine.

ΔAaP_{O_2} and $\dot{Q}_{Va}/\dot{Q}_t$

Tables 2a, 2b and 2c show individual values for PA_{O_2}, Pa_{O_2}, ΔAaP_{O_2}, $\dot{Q}_{Va}/\dot{Q}_t(\%)$, V_D, V_T and f, sitting and lying during air-breathing, O_2-breathing and breathing O_2 in deep breaths. The lying-sitting differences are also shown.

In table 3 mean values of ΔAaP_{O_2} and $\dot{Q}_{Va}/\dot{Q}_t$ in each situation are shown. The subjects are grouped according to age and to the CV-ERV difference. The progression of the lying-sitting differences through groups A-C and 1-3 is similar for air breathing, O_2 breathing and during deep breaths of O_2. For ΔAaP_{O_2}, for example, the differences are: Air, -6.2, +9.4, -1.7; O_2, +4.0, +21.4, +12.7; O_2 in deep breaths, -5.4, +5.0, -2.6, in groups A, B and C respectively. This is shown graphically in figure 1 for $\dot{Q}_{Va}/\dot{Q}_t$. Figures 2-9 show plots of ΔAaP_{O_2}, and $\dot{Q}_{Va}/\dot{Q}_t$ against age and against the difference CV-ERV for both air and O_2 breathing, sitting and lying. These illustrate how in the sitting position ΔAaP_{O_2} and $\dot{Q}_{Va}/\dot{Q}_t$ increase linearly with age but when supine this is not so. ΔAaP_{O_2} and $\dot{Q}_{Va}/\dot{Q}_t$ both increase linearly with the CV-ERV difference when either air or O_2 is breathed and the correlation is closest in the supine position (table 4).

The non-linearity of the increase in ΔAaP_{O_2} and $\dot{Q}_{Va}/\dot{Q}_t$ with age when supine indicates that predicting normal values from age in this position is unsatisfactory and likely to be misleading. In each case (3a, 5a, 7a, 9a) there was no significant difference, by unpaired t-test, between the subjects of groups B and C but the values for groups B and C were significantly higher than for group A, often highly so ($2P < 0.001$). Also the distribution on age in figures 3, 5, 7 and 9 is markedly heteroscedastic; this was confirmed by F-tests between variances for group A and groups B and C.

Table 2a PAO_2, PaO_2, $\Delta AaPO_2$, $\dot{Q}va/\dot{Q}t$, V_D, V_T and f sitting and supine breathing air, O_2 and O_2 in deep breaths.

Subject	Position	PAO_2			PaO_2			$\Delta AaPO_2$			$\dot{Q}va/\dot{Q}t$ %			V_D		V_T		f	
		Air	O_2	O_2DB	Air	O_2	O_2DB	Air	O_2	O_2DB	Air	O_2	O_2DB	Air	O_2	Air	O_2	Air	O_2
GROUP A																			
1. H.R.	S	97.9	655	668	92.9	636	647	5.0	18.5	21	1.52	1.16	1.28	91	102	574	561	11.00	12.17
	L	98.8	654	669	97.0	639	667	1.8	15.3	2	0.74	1.31	0.12	108	118	602	589	11.67	12.17
	L-S							-3.2	-3.2	-19	-0.78	0.15	-1.16						
2. T.W.	S	95.0	658	670	98.9	641	654	-3.9	16.9	16.0	-1.0	1.04	0.98	175	171	609	488	10.00	12.67
	L	98.3	660	671	104	655	676	-5.5	5.1	-5.0	-1.77	0.44	-0.44	117	104	472	485	13.33	13.34
	L-S							-1.6	-11.8	-21.0	-0.77	-0.6	-1.42						
3. B.McL.	S	115	678	685	111	681	689	4.3	-3.2	-4	0.77	-0.19	-0.25	185	184	550	558	22.67	20.84
	L	105	676	685	104	644	660	1.0	31.9	25	0.30	2.74	2.15	223	163	659	643	17.50	18.34
	L-S							-3.3	35.1	29	-0.47	2.93	2.40						
4. B.B.	S	130	694	701	127	694	696	2.9	-0.3	5	0.34	0	0.3	181	153	592	529	30.17	24.00
	L	126	693	699	129	705	710	-3.3	-12.4	-11	-0.64	-1.06	-0.97	155	146	590	550	23.67	26.84
	L-S							-6.2	-12.1	-16	-0.98	-1.06	-1.27						
5. H.W.	S	106	663	675	100	654	632	5.4	9.3	43	1.23	0.55	2.58	121	153	395	393	17.34	20.33
	L	111	663	677	114	661	694	-2.3	2.1	-17	-0.59	0.18	-1.52	125	123	425	377	17.50	16.67
	L-S							-7.7	-7.2	-60	-1.82	-0.37	-4.10						
6. C.B.	S	97.2	661	668	91.0	656	636	6.2	4.7	32	1.70	0.31	1.93	115	129	350	453	12.83	11.17
	L	96.9	661	669	98.8	654	625	-1.9	7.1	44	-0.68	0.61	3.73	88	124	314	473	12.34	11.84
	L-S							-8.1	2.4	12	-2.38	0.3	1.8						
7. R.K.	S	113	680	686	104	663	688	9.7	16.8	-2.0	1.76	1.03	-0.12	115	111	491	426	14.33	16.34
	L	108	676	686	105	655	683	2.4	20.7	3.0	0.65	1.81	0.26	85	89	443	440	10.84	11.67
	L-S							-7.3	3.9	5.0	-1.11	0.78	0.38						
8. M.C.	S	101	670	680	96.4	641	691	5.0	29.0	-11	1.22	1.75	0.68	156	161	548	631	10.17	10.00
	L	99.6	669	681	107	615	665	-7.4	54.4	16	-2.51	4.53	1.38	92	129	505	629	9.00	9.59
								-12.4	25.4	27	-3.73	2.78	2.06						

S, sitting; L, lying supine; DB, deep breaths.

Table 2b PAO_2, PaO_2, $\Delta AaPO_2$, $\dot{Q}va/\dot{Q}t$, V_D, V_T and f sitting and supine breathing air, O_2 and O_2 in deep breaths.

Subject	Position	PAO_2			PaO_2			$\Delta AaPO_2$			$\dot{Q}va/\dot{Q}t$ %			V_D		V_T		f	
		Air	O_2	O_2DB	Air	O_2	O_2DB	Air	O_2	O_2DB	Air	O_2	O_2DB	Air	O_2	Air	O_2	Air	O_2
GROUP B																			
9. R.L.	S	110	665	676	110	663	633	0.1	1.6	43	0.02	0.12	2.57	284	221	833	703	13.83	14.50
	L	115	671	680	96.9	663	644	18.1	8.4	36	5.15	0.70	3.05	319	318	1026	1117	13.00	11.50
	L-S							18.0	6.8	-7.0	5.13	0.58	0.48						
10. K.H.	S	101	670	683	86.9	669	647	13.7	1.3	36	4.45	0.06	2.17	116	152	512	613	13.67	14.33
	L	113	672	682	86.3	626	669	26.4	46.5	13	8.91	3.90	1.13	208	198	1038	742	9.50	9.67
	L-S							12.7	45.2	-23	4.46	3.84	-1.04						
11. P.M.	S	108	672	676	91.1	605	651	16.6	67.1	25	4.22	3.97	1.51	134	119	463	407	19.17	17.50
	L	121	686	686	90.8	627	645	29.9	59.1	41	7.42	4.92	3.47	113	189	669	885	18.50	20.50
	L-S							13.3	-8.0	16	3.2	0.95	1.96						
12. C.C.	S	114	677	683	98.2	621	630	15.4	56.2	53	3.12	3.01	3.17	48.8	58.7	580	613	12.69	11.84
	L	120	681	685	102	631	689	13.4	50.5	-4	4.34	4.23	-0.35	19.3	90	1161	859	8.67	10.99
	L-S							3.0	-5.7	-57	1.22	1.22	-3.52						
13. B.M.	S	114	672	673	93.2	603	679	20.3	69.2	-6	4.28	4.08	-0.37	196	154	737	529	12.67	16.00
	L	115	665	674	83.2	451	556	31.3	214.5	118	9.96	16.00	9.42	152	143	724	602	10.00	9.34
	L-S							11	145	124	5.68	11.92	9.79						
14. M.C.	S	117	683	682	107	612	631	10.1	70.7	51	1.57	4.18	3.04	200	264	855	1050	11.17	11.00
	L	107	679	681	90.1	624	652	16.9	54.6	29	5.36	4.61	2.48	86	163	519	759	9.84	10.83
	L-S							6.8	-16.1	-22	3.79	0.43	-0.56						
15. M.W.	S	106	674	681	92.7	608	611	13.7	66.3	70	2.89	3.90	4.12	157	180	475	517	16.67	14.77
	L	110	675	683	88.5	592	601	21.1	83.1	82	6.22	6.80	6.72	126	163	477	593	15.17	15.00
	L-S							7.4	16.8	12	3.33	2.90	2.60						
16. B.L.	S	104	669	674	95.1	615	665	8.6	53.8	9	1.90	3.21	0.55	111	132	336	348	22.92	26.83
	L	99.5	669	670	95.8	628	664	3.7	40.7	6	1.22	3.47	0.52	108	114	351	421	15.67	16.75
	L-S							-4.9	-13.1	-3	-0.68	0.26	-0.03						

S, sitting; L, lying supine; DB, deep breaths.

Table 2c PAO_2, PaO_2, $\Delta AaPO_2$, $\dot{V}a/\dot{Q}t$, V_D, V_T and f sitting and supine breathing air, O_2 and O_2 in deep breaths.

Subject	Position	PAO_2			PaO_2			$\Delta AaPO_2$			$\dot{V}a/\dot{Q}t$ %			V_D		V_T		f	
		Air	O_2	O_2DB	Air	O_2	O_2DB	Air	O_2	O_2DB	Air	O_2	O_2DB	Air	O_2	Air	O_2	Air	O_2
GROUP C																			
17.P.L.	S	107	677	684	83.7	602	637	22.9	75.0	47	5.87	4.44	2.83	164	183	400	408	19.17	20.50
	L	113	679	684	87.0	615	639	25.6	63.7	45	7.56	5.36	3.82	147	159	446	411	17.00	20.00
	L-S							2.7	-11.3	-2	1.69	0.92	0.99						
18.M.S.	S	102	659	670	84.3	579	620	18.1	80.4	50	5.91	4.70	2.98	329	403	751	814	14.00	15.50
	L	96.8	658	670	79.7	507	599	17.1	151.4	71	9.70	11.77	5.87	275	360	850	976	9.00	9.50
	L-S							-1.0	71.0	21	3.79	7.07	2.89						
19.R.H.	S	117	670	677	90.8	584	616	26.3	85.8	61	5.15	5.05	3.63	386	304	1852	1246	5.67	7.33
	L	126	677	681	105	687	701	21.1	-10.4	-20	4.46	-0.89	-1.79	392	357	2020	1668	8.00	8.84
	L-S							-5.2	-96.2	-81	-0.69	-5.94	-5.42						
20.P.P.	S	103	676	682	94.8	655	681	8.2	21.1	1	1.93	1.28	.06	229	274	658	836	15.67	16.00
	L	118	680	688	109	628	690	9.0	52.0	-2	1.90	4.37	-0.17	265	260	904	949	15.00	14.50
	L-S							0.8	30.9	-3	-0.03	3.09	-0.23						
21.E.S.	S	119	671	682	106	681	738	12.8	-9.6	-56	2.14	-0.62	-3.58	160	174	448	492	15.34	11.00
	L	121	676	683	110	616	691	10.7	60.1	-8	2.29	5.04	-0.71	100	104	299	292	24.17	23.00
	L-S							-2.1	69.7	48	0.15	5.66	2.87						
22.C.V.	S	107	668	679	84.6	625	667	22.6	43.0	12	6.57	2.59	0.73	107	106	368	326	17.30	17.30
	L	105	669	677	81.9	606	647	23.4	63.2	30	10.26	5.41	2.51	99.7	114	311	362	18.00	20.20
								0.8	20.2	18	3.69	2.82	1.78						
23.M.C.	S	114	679	676	86.6	631	644	27.7	48.0	32	6.01	2.88	1.93	142	160	439	485	19.00	16.33
	L	113	679	683	94.8	622	662	17.7	57.3	21	4.89	3.40	1.69	162	171	695	662	11.67	13.00
	L-S							-10	9.3	-11	-1.12	0.52	-0.24						
24.E.S.	S	116	673	684	76.0	505	604	40.0	168	80	9.66	9.45	4.70	120	113	366	300	22.00	22.00
	L	116	674	682	75.4	498	613	40.2	176	69	14.43	13.58	5.98	140	118	438	352	19.50	21.00
								0.2	8	-11	4.77	4.13	1.28						

S, sitting; L, lying supine; DB, deep breaths.

Table 3. CV, ERV, ΔAaP_{O_2} and $\dot{Q}va/\dot{Q}t$ sitting, supine, breathing air and breathing O_2.

Grouping	Position	CV (ml)	ERV (ml)	ΔAaP_{O_2} (mm Hg) Air	O_2	O_2DB	$\dot{Q}va/\dot{Q}t$ (%) Air	O_2	O_2DB
Group A	S	368 (143)	1610 (440)	4.3 (3.9)	11.5 (10.8)	12.5 (18.8)	0.94 (0.92)	0.71 (0.65)	0.75 (1.14)
n = 8	L	-	976 (364)	-1.9 (3.5)	15.5 (20.6)	7.1 (20.3)	-0.56 (1.14)	1.32 (1.72)	0.59 (1.74)
	L-S			-6.2 (3.5)	4.0 (17.4)	-5.4 (29.7)	-1.50 (1.09)	0.61 (1.49)	-0.16 (2.23)
Group B	S	791 (225)	1177 (392)	12.3 (6.2)	48.3 (29.5)	35.1 (24.8)	2.81 (1.56)	2.82 (1.73)	2.10 (1.47)
n = 8	L	-	562 (248)	20.7 (8.9)	69.7 (62.1)	40.1 (41.0)	6.07 (2.75)	5.58 (4.54)	3.31 (3.29)
	L-S			8.4 (7.1)	21.4 (53.9)	5.0 (53.3)	3.26 (2.10)	2.76 (3.91)	1.21 (3.94)
Group C	S	641 (374)	983 (666)	22.3 (9.8)	64.0 (53.0)	28.4 (42.6)	5.41 (2.48)	3.72 (3.00)	1.66 (2.60)
n = 8	L	-	589 (493)	20.6 (9.8)	76.7 (59.3)	25.8 (34.5)	6.94 (4.35)	5.93 (4.67)	2.15 (2.95)
	L-S			-1.7 (4.1)	12.7 (52.8)	-2.6 (37.5)	1.53 (2.29)	2.21 (4.03)	0.49 (2.67)
Group 1	S	481 (320)	1466 (580)	10.4 (9.5)	30.3 (28.2)	18.9 (21.8)	2.50 (2.38)	1.81 (1.65)	1.14 (1.31)
n = 14	L	-	920 (381)	5.5 (10.3)	34.2 (42.2)	11.6 (25.1)	1.92 (4.06)	2.68 (3.30)	0.95 (2.12)
	L-S			-4.9 (4.0)	3.9 (37.2)	-7.3 (31.8)	-0.58 (2.02)	0.87 (2.92)	-0.19 (2.41)
Group 2	S	768 (227)	1105 (253)	14.0 (6.9)	49.6 (33.6)	28.4 (40.9)	3.01 (1.82)	2.89 (1.99)	1.66 (2.51)
n = 8	L	-	461 (232)	21.5 (7.0)	74.2 (60.5)	42.3 (41.7)	6.05 (2.33)	5.96 (4.41)	3.49 (3.37)
	L-S			7.5 (6.5)	24.6 (55.9)	13.9 (53.8)	3.04 (1.91)	3.07 (1.91)	1.83 (3.82)
Group 3	S	760	390	26.9	84.7	58.0	7.06	4.76	3.44
n = 2	L		223	33.3	111.3	41.0	11.67	8.74	3.56
	L-S			6.4	26.6	-17.0	4.61	3.98	0.12

Groups A, B and C according to age as defined in the text. Groups 1-3 are based on CV and ERV: 1, CV less than ERV sitting and supine; 2, CV less than ERV sitting but greater supine; 3, CV greater than ERV sitting and supine. S, sitting; L, lying supine; O_2DB, O_2 breathed in deep breaths (see text).

All values given are means, with standard deviations in brackets.

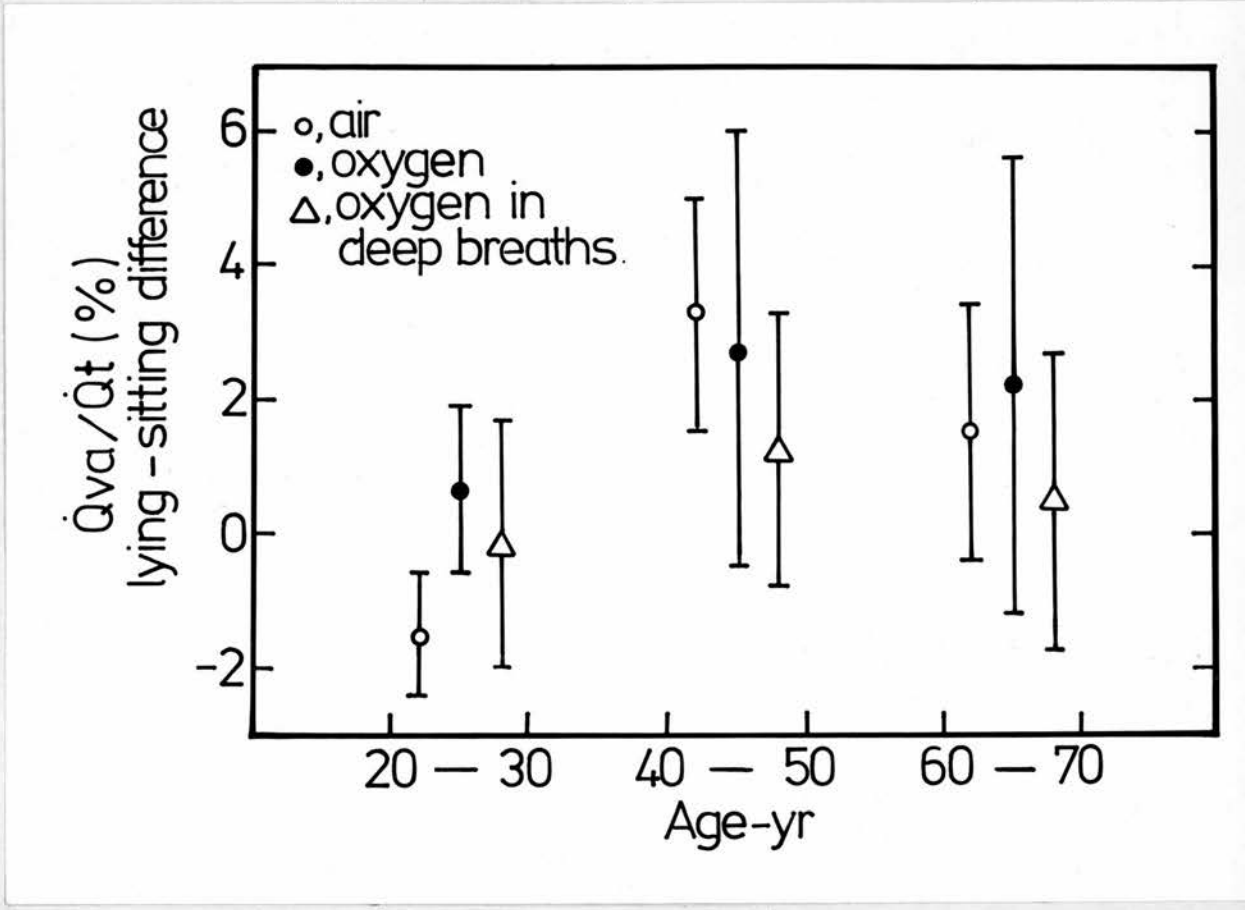
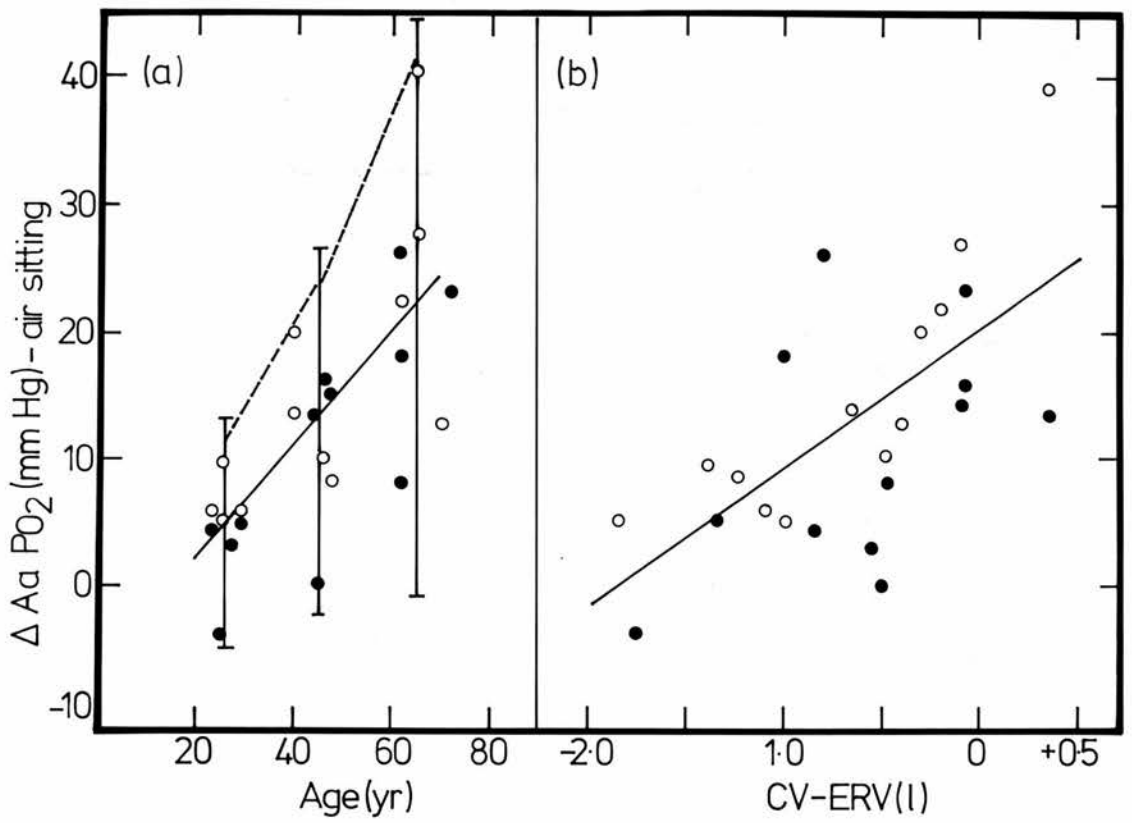


Figure 1. Lying-sitting differences in venous admixture in groups A, B and C. Mean values for the age groups are shown and the bars represent 95%-confidence intervals of the means.

Figure 2. Alveolar-to-arterial oxygen-tension gradient (ΔAaP_{O2}), sitting, breathing air plotted against (a) age (r, 0.7184; 2P < 0.001) and (b) closing volume minus expiratory reserve volume (CV-ERV) (r, 0.6507; 2P < 0.001). Closed circles men, open circles women. The continuous oblique lines are the respective regression lines for all values. In (a) the 95%-confidence interval is shown as a bar at the mean of each age-group. The dashed line joins the upper, single-sided 95%-confidence limits for the three age-groups.

Figure 3. ΔAaP_{O2}, supine, breathing air, plotted against (a) age (r, 0.6706; 2P <0.001) and (b) CV-ERV (r, 0.7947; 2P < 0.001). Conventions as in figure 2.


(a)
(b)
Δ Aa PO2 (mm Hg) - air sitting
40
30
20
10
0
-10
20
40
60
80
Age (yr)
-2·0
1·0
0
+0·5
CV-ERV (l)

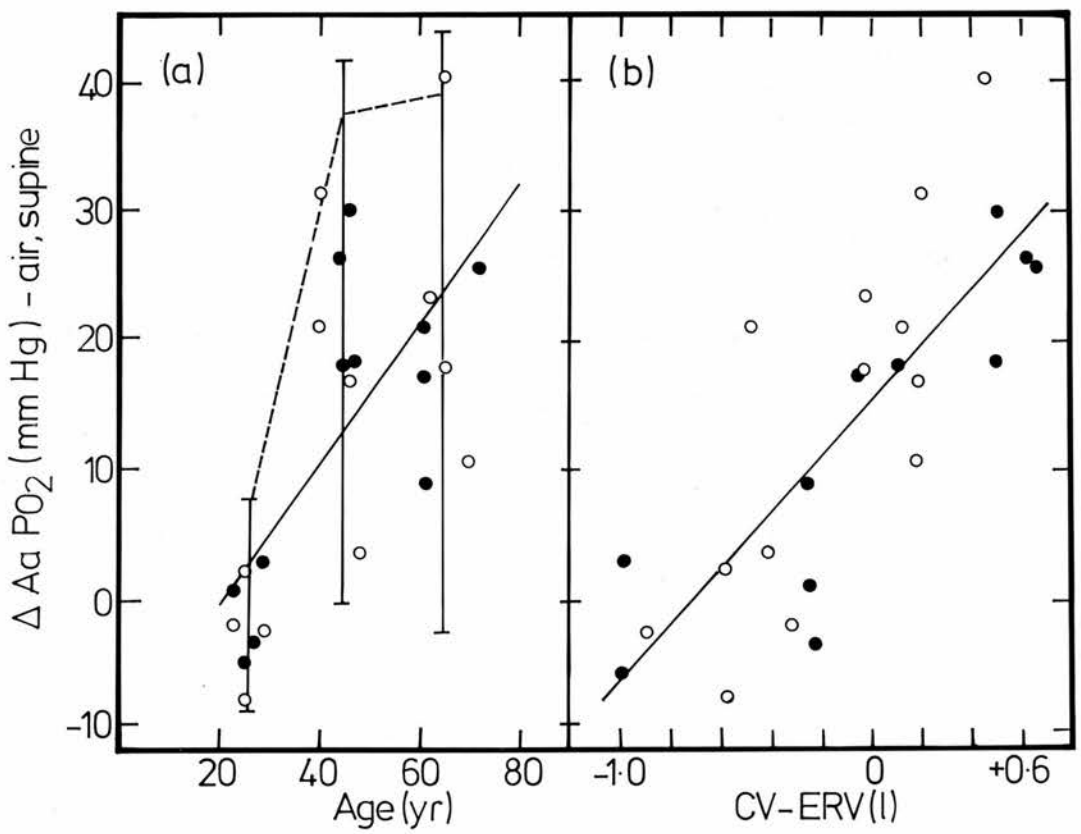
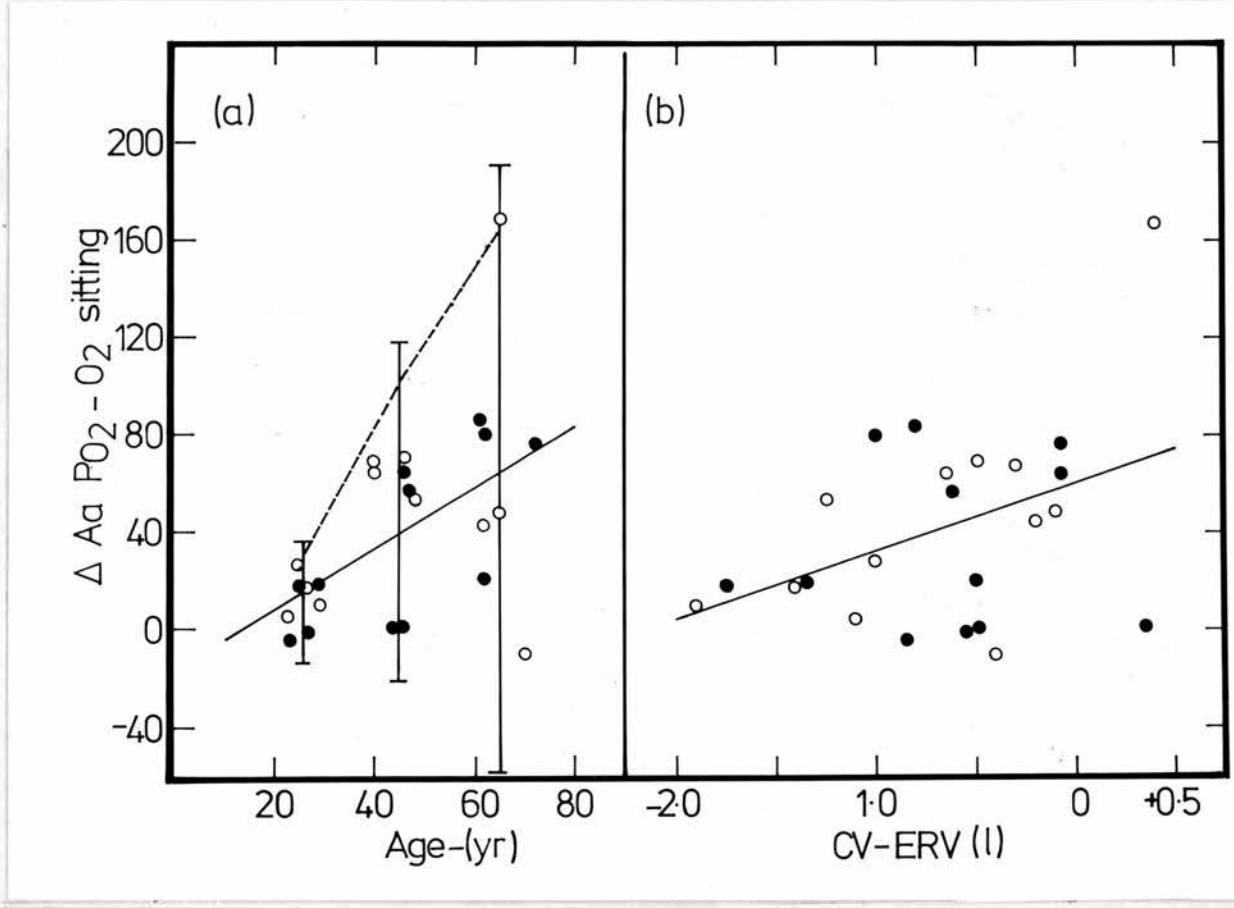

(a)
(b)
Δ Aa PO2 (mm Hg) - air, supine
40
30
20
10
0
-10
20
40
60
80
Age (yr)
-1·0
0
+0·6
CV-ERV (l)

Figure 4. ΔAaP_{O_2}, sitting, breathing O_2 plotted against (a) age (r, 0.5075; $2P < 0.05$) and (b) CV-ERV (r, 0.4100; $2P < 0.05$). Conventions as in figure 2.

Figure 5. ΔAaP_{O_2}, supine, breathing O_2, plotted against (a) age (r, 0.3956; not significant) and (b) CV-ERV (r, 0.4879; $2P < 0.05$). Conventions as in figure 2.


(a)
(b)
200
160
120
80
40
0
-40
Δ Aa P_{O_2} - O_2 sitting
20
40
60
80
Age-(yr)
-2·0
1·0
0
+0·5
CV-ERV (l)

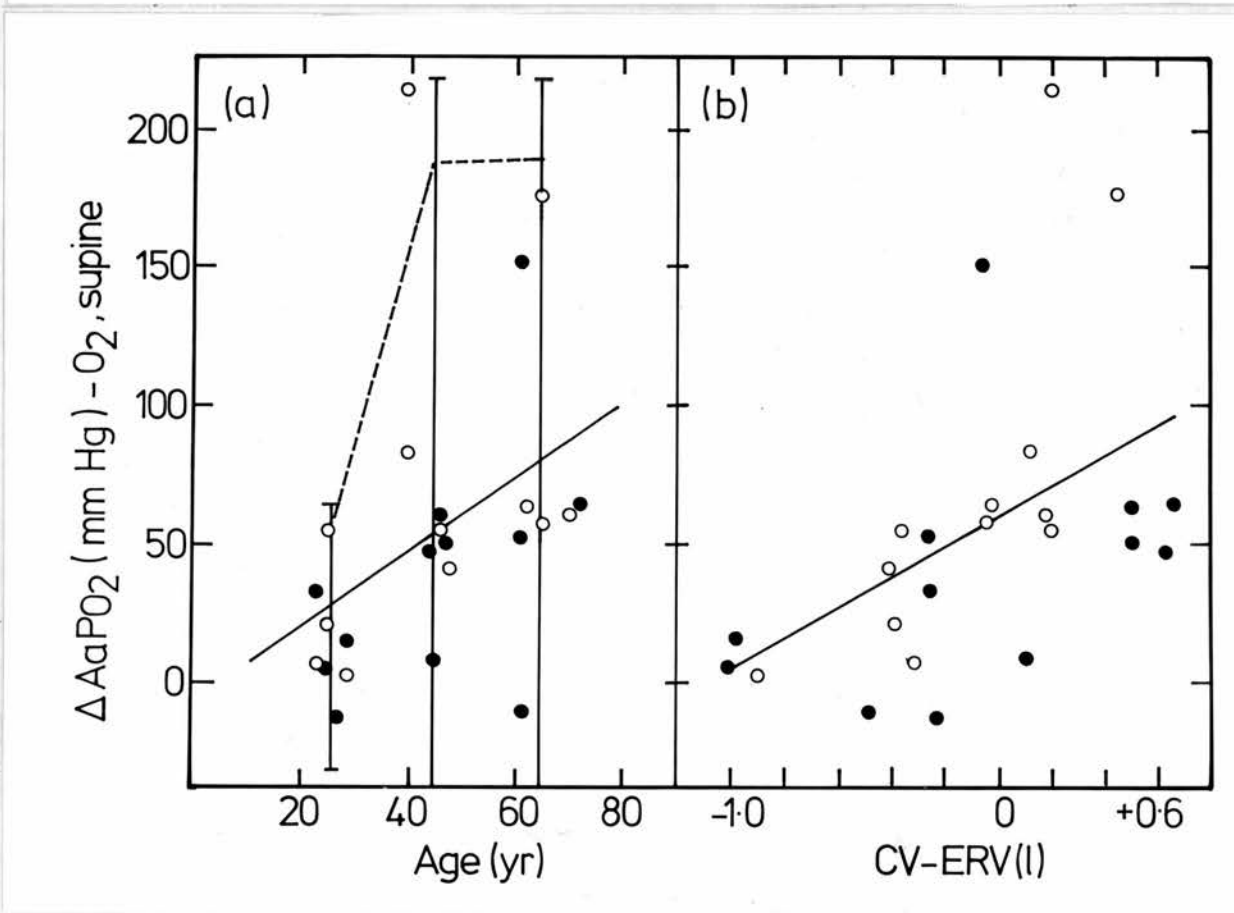
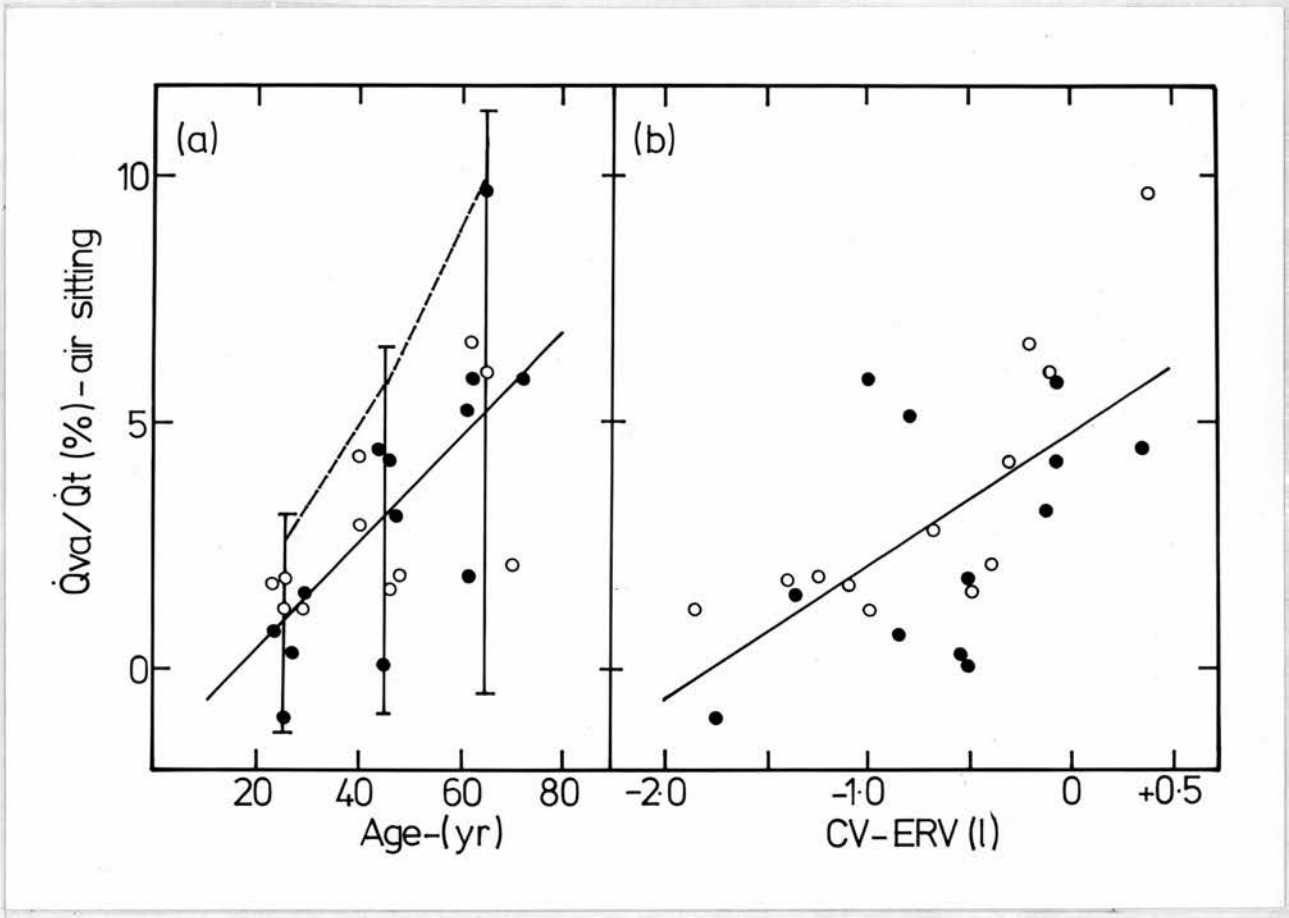

(a)
(b)
200
150
100
50
0
Δ Aa P_{O_2} (mm Hg) - O_2, supine
20
40
60
80
Age (yr)
-1·0
0
+0·6
CV-ERV(l)

Figure 6. Venous admixture ($\dot{Q}va/\dot{Q}t$), as a percentage of cardiac output, sitting, breathing air, plotted against (a) age (r, 0.7085; $2P < 0.001$) and (b) CV-ERV (r, 0.6473; $2P < 0.001$). Conventions as in figure 2.

Figure 7. $\dot{Q}va/\dot{Q}t$, supine breathing air, plotted against (a) age (r, 0.6480; $2P < 0.001$) and (b) CV-ERV (r, 0.7323; $2P < 0.001$). Conventions as in figure 2.


(a)
(b)
10
5
0
V̇va/V̇t (%) - air sitting
20
40
60
80
Age-(yr)
-2·0
-1·0
0
+0·5
CV-ERV (l)

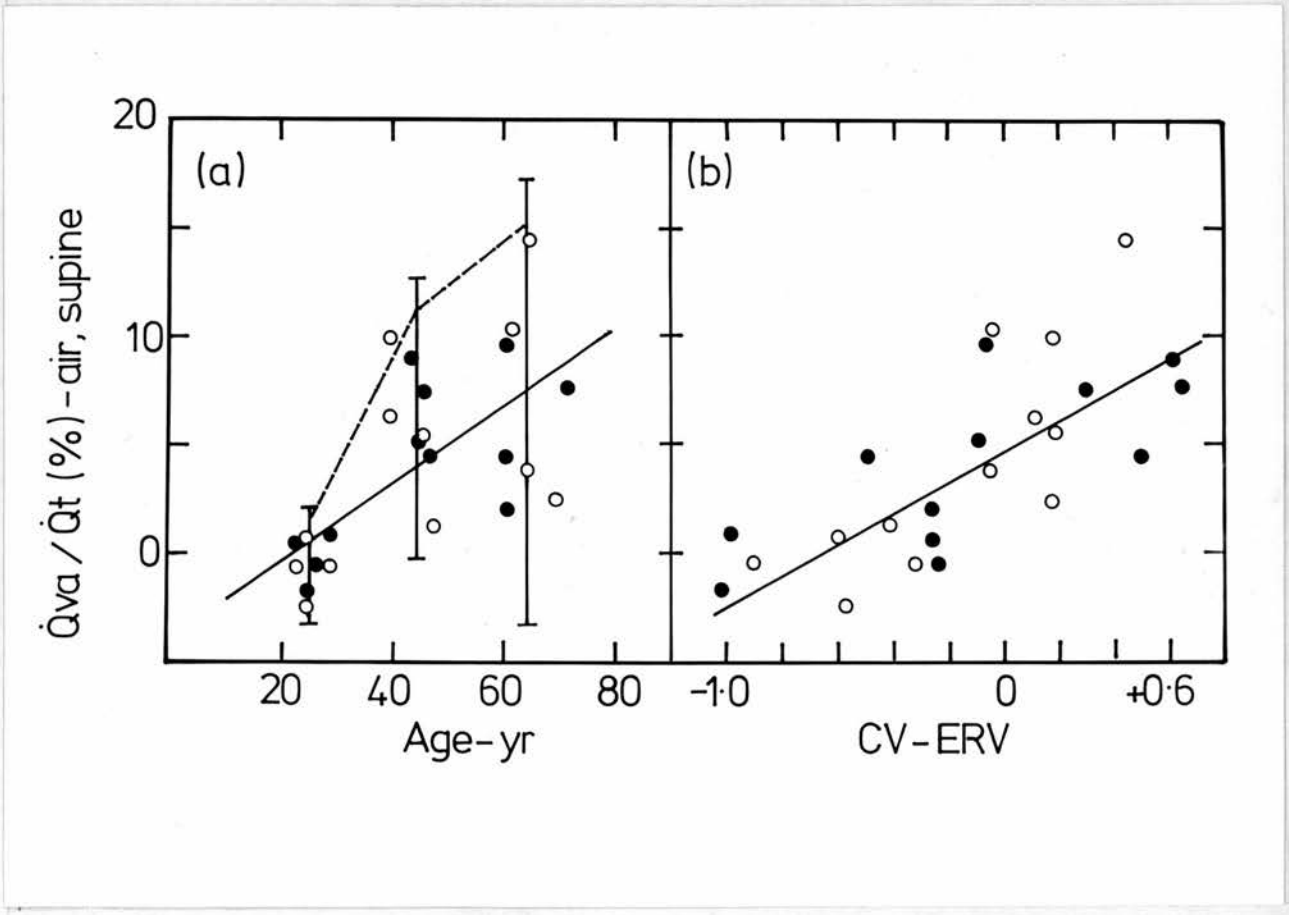
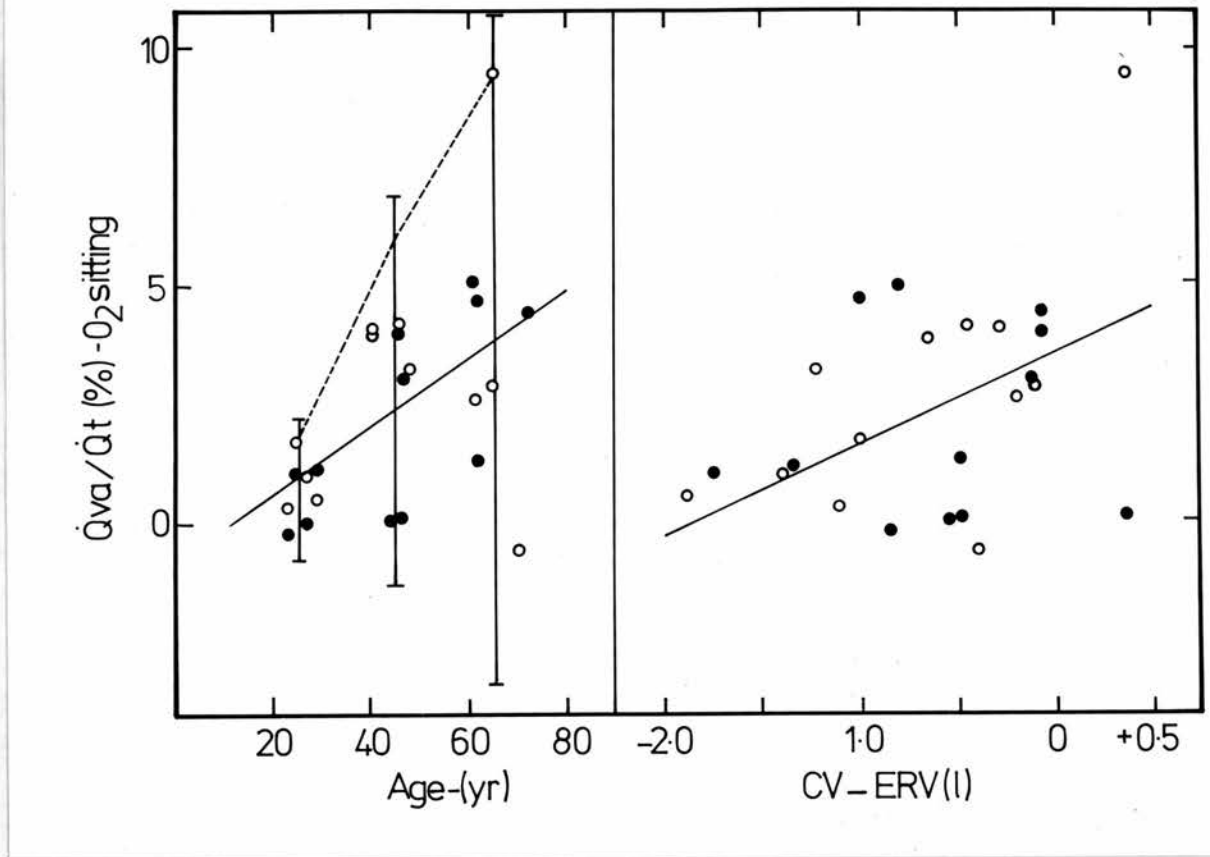

(a)
(b)
20
10
0
V̇va / V̇t (%) - air, supine
20
40
60
80
Age-yr
-1·0
0
+0·6
CV-ERV

Figure 8. $\dot{Q}va/\dot{Q}t$, sitting, breathing O_2, plotted against (a) age (r, 0.5077; $2P < 0.05$) and (b) CV-ERV (r, 0.4874; $2P < 0.05$). Conventions as in figure 2.

Figure 9. $\dot{Q}va/\dot{Q}t$, supine, breathing O_2, plotted against (a) age (r, 0.3917; not significant) and (b) CV-ERV (r, 0.5031; $2P \ll 0.05$). Conventions as in figure 2.


10
5
0
$\dot{Q}va/\dot{Q}t$ (%) - O_2 sitting
20
40
60
80
Age-(yr)
-2·0
1·0
0
+0·5
CV – ERV (l)

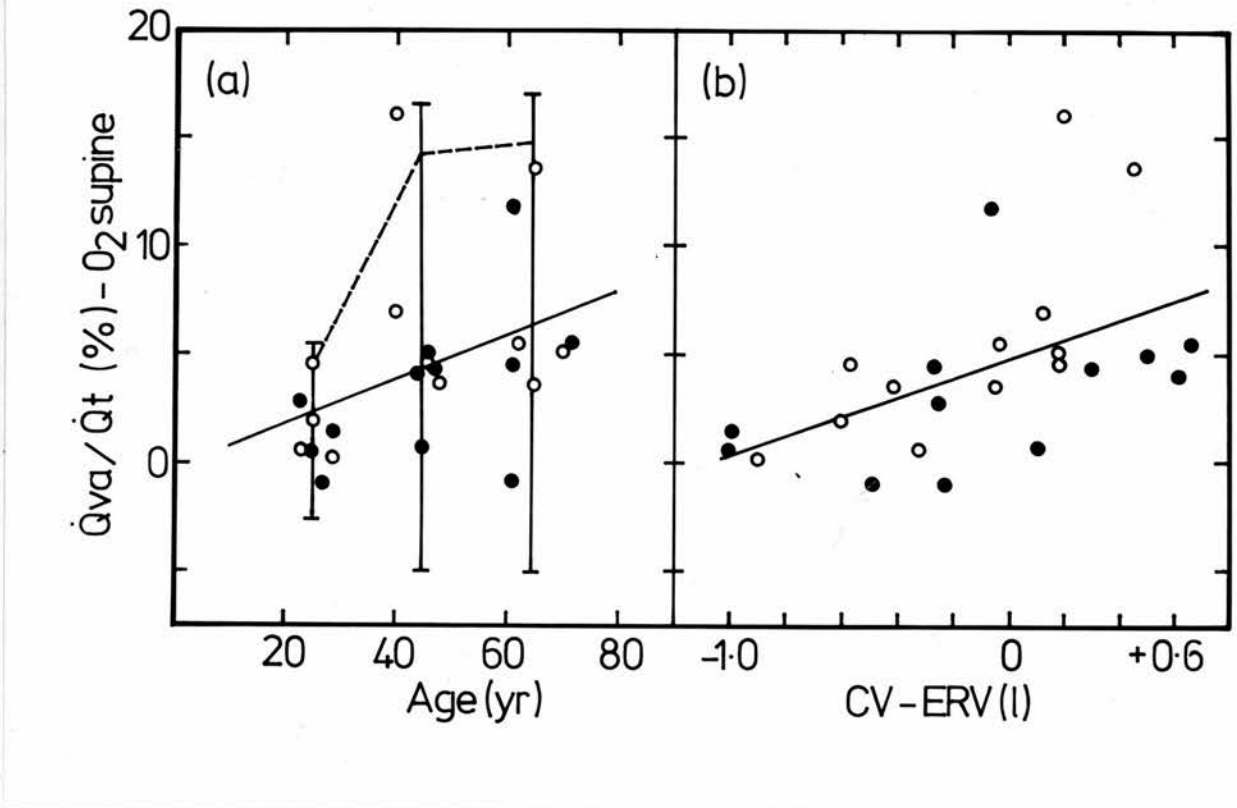

20
10
0
$\dot{Q}va/\dot{Q}t$ (%) - O_2 supine
(a)
(b)
20
40
60
80
Age (yr)
-1·0
0
+0·6
CV - ERV (l)

Table 4 lists the correlation coefficients calculated for all sets of data. In the sitting position both $\Delta AaPO_2$ and $\dot{Q}_{Va}/\dot{Q}_t$ were better correlated with age than with CV-ERV on both air and O_2, but the converse was true in the supine position (table 4, (1) and (2)). Since CV-ERV was positively correlated with age (sitting, $r = 0.6053$, $2P < 0.01$; supine, $r = 0.5620$, $2P < 0.01$) it was possible that the simple correlations with one or other of these variables might have been to some extent spurious. A multiple-regression analysis was therefore carried out to separate the effects of age and CV-ERV, and the results are shown in table 4 (3). The differences in correlation with CV-ERV compared with age are more marked than in the case of simple correlations. In particular, in the supine position, the apparently highly-significant correlations with age in the simple regressions became insignificant as partial correlations.

Within subjects, $\Delta AaPO_2$ and $\dot{Q}_{Va}/\dot{Q}_t$ were well correlated between the sitting and supine postures and between air- and O_2-breathing. Breathing air, sitting and supine, $\Delta AaPO_2$ showed a correlation coefficient (r) of 0.8000, and breathing O_2 0.6416. Sitting, $\Delta AaPO_2$ showed $r = 0.7982$ between air- and O_2-breathing, and in the supine position $r = 0.6435$. For $\dot{Q}_{Va}/\dot{Q}_t$ the respective correlation coefficients, in the same order, were 0.8465, 0.6343, 0.7631 and 0.7327. All these correlations were significant at the 0.001 level. They show that, in general, subjects with high venous admixtures under one circumstance tend to have high admixtures under the others.

Table 4. Correlation of ΔAaP_{O_2} and $\dot{Q}va/\dot{Q}t$ with age and CV-ERV.

	ΔAaP_{O_2}				$\dot{Q}va/\dot{Q}t$			
	Sitting		Supine		Sitting		Supine	
	Air	O_2	Air	O_2	Air	O_2	Air	O_2
(1) Age								
r	0.7184	0.5075	0.6706	0.3956	0.7085	0.5077	0.6480	0.3917
2P	<0.001	<0.05	<0.001	NS	<0.001	<0.05	<0.001	NS
(2) CV-ERV								
r	0.6507	0.4100	0.7947	0.4879	0.6473	0.4874	0.7323	0.5031
2P	<0.001	<0.05	<0.001	<0.05	<0.001	<0.05	<0.001	<<0.05
(3) Age and CV-ERV								
r(age)	0.5369	0.3572	0.4460	0.1628	0.5219	0.3645	0.3957	0.1573
2P	<0.05	NS	NS	NS	<0.05	NS	NS	NS
r(CV-ERV)	0.3898	0.1499	0.6768	0.3502	0.3888	0.1341	0.5835	0.3700
2P	NS	NS	<0.01	NS	NS	NS	<<0.05	NS
r(multiple)	0.7679	0.5237	0.8386	0.5082	0.7598	0.5206	0.7794	0.5227
2P	<0.01	<0.05	<<0.01	<0.05	<0.01	<0.05	<<0.01	<0.05

Physiological dead space volume (V_D)

Values of physiological dead space were not significantly different for men and women and for air and O_2 breathing.

In comparing the sitting with the supine position, the effect of changes in breathing pattern upon V_D must be taken into account. In this study, V_T increased and f decreased significantly on lying down in groups B and C; the first would tend to increase, the second to decrease V_D. The net result would depend on the magnitude of changes in V_T and f and on their relative weighting. Table 5 summarizes the data; the predicted change in V_D from sitting to lying was calculated assuming that the resting sitting equation of Harris et al. (1973) applies to the lying position in so far as the effects of V_T and f are concerned. The actual change in V_D from sitting to lying was significant only in group A. When compared with the change expected from changes in V_T and f, it became significant in groups B and C as well, and was of about the same size in all three groups (11, 12 and 15% respectively).

Table 5. Tidal volume (V_T), frequency (f) and deadspace volume (V_D) in sitting (S) and lying (L) positions in Groups A, B and C.

Group	V_T(ml)		f(breaths/min)		V_D(ml)		Change	Predicted change
	S	L	S	L	S	L	L-S	L-S
A	509	512 (NS)	16.0	14.8 (NS)	144	124 (2P<0.02)	-20(-14%)	-5(-3%)
B	598	746 (2P<0.05)	15.6	12.8 (2P<0.005)	158	157 (NS)	-1(-1%)	+21(+11%)
C	637	727 (2P<0.05)	15.9	15.8 (NS)	210	202 (NS)	-8(-4%)	+25(+11%)

Discussion

Posture and closing volume

The assumption that, in the subjects of this study, CV was unaffected by posture is supported by evidence from two sources. First, additional data (Becklake, 1976) from the study described by Craig et al. (1971) show, in 22 subjects aged 21 to 78 years, no significant change by paired t-test in CV between the sitting and supine positions. Secondly, in a study of 22 healthy subjects aged 21 to 72 years in this laboratory, the same conclusion has been reached. The individual values from both studies are shown in table 6 and the paired t-tests comparing sitting and supine CV are shown in table 7. These studies cover a wide range of ages and closing volumes in 44 subjects in 2 laboratories. Although ERV changes with posture it is therefore justifiable to assume that CV does not.

Validity of calculation of $\dot{Q}_{Va}/\dot{Q}_t$

The evidence for acute changes in $\Delta a\bar{v}C_{O_2}$ on lying down has been presented in the review of the literature. In this study the pulmonary artery was not catheterized. For calculating $\dot{Q}_{Va}/\dot{Q}_t$ in the sitting position in normal subjects it seems reasonable to assume a $\Delta a\bar{v}C_{O_2}$ of 50 ml. l^{-1}, since this is a convenient round figure and is the basis of many publications. For the supine position $\Delta a\bar{v}C_{O_2}$ was assumed to be 30% less than the sitting value i.e. 35 ml. l^{-1}.

The effect of error in the assumption of supine $\Delta a\bar{v}C_{O_2}$ upon the derived value of $\dot{Q}_{Va}/\dot{Q}_t$ would vary with the size of admixture. Representative calculations show that a ±20% variation in assumed

Table 6.

Craig et al. (1971)

Subject	Sex	Age(yr)	Closing volume (ml) Sitting	Supine
D.C.	M	29	625	580
J.C.	M	31	455	525
J.W.	M	21	735	550
J.L.	M	25	820	580
W.W.	M	35	800	965
H.D.	M	37	920	895
P.M.	M	25	690	950
B.L.	M	46	1080	810
M.B.	F	47	850	810
W.J.	M	56	900	1330
M.K.	F	46	545	580
S.G.	F	55	490	700
W.L.	M	55	1065	1065
W.G.	M	47	1630	1490
R.H.	M	48	1130	1260
P.S.	M	64	1190	1230
A.B.	M	78	1170	1280
R.B.	F	68	920	790
A.L.	M	73	1400	915
J.I.	M	65	1220	1340
P.C.	F	61	820	750
H.S.	M	76	1950	1870

Rea

Subject	Sex	Age(yr)	Closing Volume (ml) Sitting	Supine
H.R.	M	30	958	608
S.W.	M	29	753	602
P.R.	M	21	877	616
T.W.	M	25	627	801
N.B.	M	33	836	1018
N.A.	M	26	672	1123
C.L.	F	25	397	491
L.W.	F	19	1100	1099
R.L.	M	40	1076	725
R.W.	M	41	848	1415
E.H.	M	52	1146	988
B.M.	F	40	707	801
M.B.	F	44	902	1064
M.C.	F	41	695	1041
E.S.	F	47	1178	879
M.S.	F	50	807	780
D.C.	F	62	435	573
D.M.	M	71	1643	1482
R.D.	M	71	1150	1345
C.H.	F	62	649	707
P.H.	F	63	402	550
T.W.	F	68	1154	1199

Table 7. Paired t-tests; closing volume sitting & supine.

	20 - 40(yr)		40 - 60(yr)		60+(yr)	
	Rea	Craig	Rea	Craig	Rea	Craig
Mean sitting	778	721	920	961	906	1239
Mean lying	795	721	962	1005	976	1168
t	-0.1850	0	-0.3746	-0.5821	-1.3613	0.9048
N	8	7	8	8	6	7

	Rea (all subjects)	Craig (all subjects)	Craig & Rea (subjects combined)
Mean sitting	864	973	919
Mean lying	905	967	935
t	-0.7736	0.1505	-0.5117
N	22	22	44

$\Delta a\bar{v}C_{O_2}$ would cause a variation in $\dot{Q}_{Va}/\dot{Q}_t$ of about ±0.8% if $\dot{Q}_{Va}/\dot{Q}_t$ is of the order of 5%. Since mean values from 8 subjects are used in interpreting the present data, this error would be reduced by a factor of 8, giving an error of about ±0.28%.

Evidence for changes in $\Delta a\bar{v}C_{O_2}$ when O_2 is breathed is also presented in the review of the literature. Our assumption that $\Delta a\bar{v}C_{O_2}$ does not change when air-breathing is changed to O_2-breathing in normal subjects is based on the work of Barratt-Boyes and Wood (1958).

Supine ΔAaP_{O_2} and closing volume

The demonstration of a direct correlation in supine subjects between ΔAaP_{O_2} and CV-ERV confirms the findings of Alexander et al. (1973) in recumbent patients breathing air before and after upper abdominal operations. Our study shows that the same relationship holds for healthy subjects breathing O_2. We have calculated a correlation coefficient of 0.6835 ($2P < 0.001$) between supine, air breathing ΔAaP_{O_2} and CV-ERV from Craig's study of normal subjects (1971).

In our subjects supine ΔAaP_{O_2} seems not to be linearly related to age nor as closely correlated with age as with CV-ERV (table 4). This suggests that factors unrelated to age are important determinants of supine admixture. We believe that an important contribution to supine ΔAaP_{O_2} is made by alveoli subject to continuous or cyclical, gravity-dependent airway closure; thus ΔAaP_{O_2} is well correlated with CV-ERV. Only the CV part of this need be age-related and when supine CV-ERV is poorly correlated with age, as in our study ($r = 0.5655$; our middle age-group was the fattest and had the lowest supine ERVs), one might not expect a high correlation between ΔAaP_{O_2} and age. In Craig's subjects (1971), supine ΔAaP_{O_2} was well

correlated with age (r = 0.7933) but CV-ERV also was closely related to age (r = 0.7660) because his older subjects tended to be the fat ones, the ones with big CVs and the low ERVs when supine.

Prediction of venous admixture in the supine position

Clinically and for the CPBP operative study it would have been useful to be able to predict the normal range of ΔAaP_{O_2} and of $\dot{Q}_{Va}/\dot{Q}_t$ to be expected in a given subject supine, as one may according to age, seated at rest (Harris et al., 1974) and according to weight-adjusted O_2-uptake during treadmill exercise (Harris et al., 1976). In the supine position a prediction of this kind seems impracticable on the present evidence. The insignificant partial correlations of ΔAaP_{O_2} and $\dot{Q}_{Va}/\dot{Q}_t$ with age, and the distributions shown in figures 2a, 4a, 6a, 8a, make age an unsatisfactory predictor. Prediction might be made on the basis of CV-ERV, but this would make the admixture, in a patient with an abnormal CV-ERV, appear normal. It is not clear how far our subjects represent the general population of healthy people; the weight/height ratios of group B were higher than those of group C. It may be that the subjects of group B were unusually unfit (they have the highest CVs and lowest supine ERVs) or group C unusually fit, or that a high weight/height ratio is a handicap in reaching the age of 60 yr.

It may be that a greater number of subjects or a 'more normal' group might have yielded data which allowed age to be used as a useful predictor of supine admixture. This seems unlikely because factors which are not age related are important in determining supine gas exchange.

Sitting ΔAaP_{O_2} and closing volume

The question remains why, in the present study, ΔAaP_{O_2} and $\dot{Q}_{Va}/\dot{Q}_t$ in sitting, air breathing subjects were age-related (table 4, (3)) when no clear correlation with CV-ERV could be shown. This might indicate that an age-related mechanism other than airway closure dominates the picture in the sitting position. Only two subjects had CV > ERV when sitting, so airway closure is unlikely to be a significant mechanism influencing gas exchange in that position and other factors may dominate. On lying, however, 10 subjects have at least measurably significant airway closure and this may swamp other factors influencing gas exchange.

The effect of change in posture on venous admixture

The results of this study confirm the conclusions of Craig et al. (1971), who showed that the postural change in ΔAaP_{O_2} and $\dot{Q}_{Va}/\dot{Q}_t$ depends upon the concomitant change in the relationship between closing volume and breathing level, in a subject breathing air. This study also shows that venous admixture during O_2-breathing, whether in normal or deep breaths, alters with posture in a similar manner, i.e. in group 1 gas exchange improved or deteriorated very little on lying; in groups 2 and 3 gas exchange deteriorated on lying (table 3).

Harris et al. (1976) have argued that $\dot{Q}_{Va}/\dot{Q}_t$ breathing O_2 in the sitting position cannot be taken as a measure of anatomical shunt, because although O_2-breathing abolishes the contribution of most alveoli with low $\dot{V}/\dot{Q}$ ratios to venous admixture, those with the lowest ratios close when O_2 is breathed and behave as a direct right-to-left shunt (Wagner et al., 1974). Even deep breaths of O_2

do not reopen all the alveoli with critically low $\dot{V}/\dot{Q}$ ratios, though mild exercise may do so (Harris et al., 1976). Breathing air, the mechanism of the postural effects of admixture is almost certainly related to continuous or cyclical gravity-dependent airway closure (Milic-Emili et al., 1966).

It appears probable that, since postural effects on O_2-breathing gas exchange follow the same pattern as air breathing, and since O_2-breathing admixture is correlated with CV-ERV, this mechanism is important when O_2 is breathed as well as when air is breathed. It may be, then, that the alveoli which close on O_2-breathing, due to critically low $\dot{V}/\dot{Q}$ ratios, lie in the dependent zones of the lungs; they represent the lowest $\dot{V}/\dot{Q}$ ratios generated by cyclical airway closure.

Comparison with previous work

Table 8 allows comparison to be made between the results of this investigation and previously published data. Breathing air the main point to be noted is the (insignificantly) negative value for lying ΔAaP_{O2} in group A, in contrast to the positive values of other workers. In subjects of comparable age, however, only one study, Riley et al. (1959), showed a significantly positive value; this was based on the bubble-equilibration method for measurement of arterial PO_2 and may have contained a systematic error. The essentially zero admixture in young subjects, breathing air in the supine position, suggests that in these circumstances the lungs behave ideally, presumably because ventilation and perfusion and especially $\dot{V}/\dot{Q}$ ratios, become almost uniform on lying down. Breathing O_2, the present values of ΔAaP_{O2} are notably higher than those of Cole and

Table 8. Comparison of present data for alveolar-arterial O_2-tension difference (ΔAaP_{O_2}) with published work.

Reference	Number of subjects	Age(yr)	ΔAaP_{O2} (mm Hg)			
			Air		Oxygen	
			Sitting	Supine	Sitting	Supine
Riley et al. (1959)	5*	21-31	10.8 (3.5)	-		
	7	21-34	-	7.4 (2.5)		
Raine & Bishop (1963)	32	<40	5.9 (5.2)	-		
	14	<40	-	6.4 (5.6)		
	17	>39	16.7 (4.8)	-		
	7	>39	-	15.6 (6.8)		
Cole & Bishop (1963)	8	20-29	7.9 (4.5)	9.2 (4.7)	7.9 (13.1)	4.1 (11.0)
	8	50-59	14.9(10.4)	14.2 (7.3)	21.6 (34.2)	20.8 (19.1)
Malmberg (1966)	18	19-58	10.0 (6.6)	10.5 (9.3)		
Cardus (1967)	7	21-25	-	9.0 (6.7)		
Trimble et al. (1972)	7	19-24	-	9.9 (6.5)		
Harris et al.(1974 & 1976)	24	20-30	6.1 (5.5)	-	30.2 (6.0)	-
	24	39-51	10.6 (6.2)	-	47.2(27.2)	-
	24	60-74	17.0 (7.7)	-	63.0(37.0)	-
Present study	8	23-29	4.3 (3.9)	-1.9 (3.5)	11.5(10.8)	15.5 (20.6)
	8	40-48	12.3 (6.2)	20.7 (8.9)	48.3(29.5)	69.7 (62.1)
	8	61-72	22.3 (9.8)	20.6 (9.8)	64.0(53.0)	76.7 (59.3)

*Subjects standing.

All values are means, with standard deviations in brackets.

Bishop (1963); this discrepancy was noted by Harris et al. (1974) and has been discussed in the review of the literature.

Physiological deadspace in the supine position

It appears that a useful prediction of a normal value can be made in the case of V_D. Table 5 shows that if V_D be predicted from age, height, V_T and f as though the subject were sitting (Harris et al., 1973), the subtraction of 12.5% will give a good estimate of the normal supine value. How far the sitting-equation is valid in the supine position has not been established.

Conclusions

The wide confidence limits for supine ΔAaP_{O2} and $\dot{Q}_{Va}/\dot{Q}_t$ in this study meant that it would be unsatisfactory to assess the normality of lung function in the group of surgical patients, according to age. Age does not seem to be linearly related to supine ΔAaP_{O2} and $\dot{Q}_{Va}/\dot{Q}_t$ suggesting that factors which are not age related are important in determining pulmonary blood-gas exchange in that position. The study provided some further insight into the mechanisms which are important in altering gas exchange when posture is changed or oxygen breathed. It seems that the relationship of closing volume to breathing level may be important in both.

PART II

The Effects of Cardiopulmonary Bypass on Respiratory Function in Man

Review of the literature

The objective of this literature review was to obtain information about:

1. Lung pathology following cardiopulmonary bypass
2. Clinical incidence of pulmonary complications following cardiopulmonary bypass
3. Pulmonary physiological changes following bypass
4. Changes in cardiac output following bypass
5. Pulmonary physiological changes following major surgery without bypass
6. Pulmonary and cardiac physiological changes due to propranolol. (As the patients going forward for coronary vein-graft surgery would be on β adrenergic blocking drugs).

The review will be made under these 6 headings.

1. Lung pathology following cardiopulmonary bypass

The use of cardiopulmonary bypass (CPBP) in open-heart surgery has been associated with many pathophysiological disturbances including pulmonary and renal abnormalities, cardiac lesions and alterations in cerebral and hepatic function. These changes have been attributed to a variety of mechanisms primarily concerned with alterations in the perfusate, such as denaturation of plasma proteins, homologous blood

reaction, particulate microemboli, unspecified toxic factors or enzymes released by blood trauma. Of these agents, platelet and leukocyte microemboli have recently been suggested as the most important mechanism. Microvascular occlusion by such aggregates has been demonstrated in both man and animals.

In a study at Duke University, Ratliff et al. (1973) described ultrastructural changes in lung biopsies before and after CPBP and discussed the cause of these changes. Lung biopsies were examined in 32 patients. They were taken five minutes before the start and five minutes after the end of CPBP. A disc oxygenator and roller pumps were used. Bypass duration varied from 35 to 260 minutes. Biopsies were examined by electron and light microscopy.

In 23 patients intravascular neutrophil polymorphonuclear leukocytes were found in increased numbers in the post-bypass biopsy. They were usually found in capillaries where they appeared to fill the vessel lumen. In five biopsies leukocytes were observed to be disintegrating. In 13 biopsies endothelial-cell swelling was more severe after CPBP. Usually if endothelial swelling was present in the pre-bypass specimen it was more severe in the post-bypass specimen. Severe endothelial damage was not observed in the absence of large numbers of polymorphonuclear leukocytes in the pulmonary vessels. Membranous pneumocytes exhibited the same type of damage as did the endothelial cells and this was again related to the number of leukocytes in the pulmonary circulation.

Light microscopy showed that the earliest consistent abnormality was interstitial oedema, the severity of which correlated with the duration of CPBP. After more than 150 minutes

interstitial and intra-alveolar haemorrhage, vascular congestion and intra-alveolar oedema became prominent. Haemorrhage began near pre-capillary arterioles. The severity of the alterations observed in the post-bypass specimens was related to the degree of abnormality in the pre-bypass specimens.

Ratliff et al. (1973) summarised the pathological changes in the lung following cardiopulmonary bypass as:

(1) Swelling of endothelial cells, of membranous pneumocytes and of mitochondria in granular pneumocytes.

(2) Interstitial oedema; interstitial haemorrhage.

(3) Engorgement of the pulmonary vascular bed.

(4) Miliary atelectasis.

They pointed out that these changes are features of the pulmonary injury associated with haemorrhagic shock, endotoxaemia, severe soft-tissue trauma and cardiopulmonary bypass. In all these conditions experiments have shown that if one lung is excluded from the circulation it is protected from injury. It seems, therefore, that something in the circulating blood is injurious to the lung.

There is increasing evidence that intravascular microaggregates of platelets and leukocytes lodge in the microcirculation and contribute to the development of 'shock lung'. Connell et al. (1973) listed the sources of such emboli during open-heart surgery:

(1) Blood collected from the pericardium and pleural spaces by the open-heart return suction lines.

(2) Homologous blood used to prime the extracorporeal circuit.

(3) Endogenous platelet and leukocyte aggregates, shown to occur during acute hypotension and trauma (Swank, 1964).

(4) Blood traumatised by the CPBP procedure.

Lodged leukocytes may disintegrate and release their granules into the pulmonary circulation producing endothelial damage, oedema and haemorrhage.

Connell et al. (1973) pointed out that in total CPBP the entire peripheral capillary bed must function as a filter for platelet and leukocyte aggregates. Such aggregates have been observed in the brain, kidneys, lungs and other organs following cardiotomy. Pulmonary microvascular embolisation could occur during CPBP by way of the bronchial arteries. Animal studies indicate that emboli filtered by the capillary beds of the body subsequently have a tendency to escape and re-enter the general circulation. These aggregates may become lodged in the lung later.

Ratliff et al. (1973) concluded that there are three critical factors in the development of respiratory insufficiency after extracorporeal circulation:

(1) The duration of CPBP.

(2) Sequestration of polymorphonuclear leukocytes in the pulmonary capillaries.

(3) The state of the lung before operation.

Their results suggested that a healthy lung was more resistant to the trauma of CPBP than a previously injured lung.

Connell et al. (1973) studied 37 patients undergoing CPBP with a bubble oxygenator and a diluted blood prime. Lung biopsies were taken five minutes before the start and approximately one hour after the end of CPBP, and examined by electron microscopy.

The post-bypass specimens revealed extensive occlusion of the capillary bed by aggregates of leukocytes in various stages of disintegration. In such areas the intralveolar septa showed

perivascular oedema. The endothelium and overlying alveolar epitheleum appeared swollen and was often ruptured. The removal of leukocyte aggregates by Dacron-wool filtration was shown to reduce the extent of these lesions. Filters were placed in the open-heart return, priming and arterial lines. The more complete the filtration the more normal the lungs appeared to be after CPBP.

Rabelo et al. (1973) explored other ways of reducing the pathological pulmonary changes associated with CPBP.

Twenty-four patients with mitral valve disease were divided into three groups according to the priming fluid used:

(a) total homologous blood

(b) total autologous blood

(c) Ringer-lactate - dextran.

Biopsies were examined by light and electron microscopy. Pathological changes in the group receiving homologous blood were similar to those reported by Ratliff (1973). Changes in the patients primed with total autologous blood or clear fluid were very much less marked. There was no relationship between the pulmonary changes and the duration of CPBP.

Hill et al. (1975) suggested that a membrane oxygenator may produce less lung damage than a bubble oxygenator.

This summary of pulmonary pathological changes associated with cardiopulmonary bypass emphasizes the difficulty of comparing studies of post-bypass pulmonary physiology. There are indications that differences in type of prime, oxygenator, filter, length of perfusion and preoperative pulmonary status may all significantly alter the degree of lung damage to be expected.

2. The clinical incidence of pulmonary complications following cardiopulmonary bypass.

Provan et al. (1966) described a careful study undertaken to determine the frequency with which respiratory complications were seen after cardiac surgery with cardiopulmonary bypass. They attempted to define factors which might predispose to the development of such complications.

They investigated 242 patients seen at the Massachusetts General Hospital from 1962 to 1964. A disc oxygenator, blood prime and moderate hypothermia (oesophageal temperature 34° to 28°C.) were used. The patients fell into five groups:

(1) congenital lesions

(2) mitral valve disease

(3) aortic valve disease

(4) multiple valve disease and

(5) miscellaneous disease.

Factors considered to be of possible relevance in the production of postoperative pulmonary complications were sought in the preoperative, operative and postoperative data.

The postoperative course was assessed from a respiratory standpoint as uncomplicated, moderately complicated or severely complicated. 'Uncomplicated' meant no respiratory problems by clinical examination, but included minor radiological abnormalities such as plate atelectasis and small pleural effusions. The latter were present in many patients without clinical signs.

'Moderately complicated' meant clinical signs of lobar or segmental collapse, requiring extra physiotherapy and/or the use of O_2 by mask. Radiological signs which did not improve, or

worsened after the second postoperative day, also placed the patient in this class.

The postoperative course was considered 'severely complicated' when the patient required frequent attention to the pulmonary condition with worsening of clinical and radiological signs despite energetic physiotherapy. The need for tracheostomy or assisted ventilation placed a patient in this group.

The overall incidence of postoperative respiratory complications was 61.5%. Of these 19.8% were severe. The highest incidence and most severe complications occured in those having double or triple valve procedures. Operations for congenital lesions were followed by the lowest incidence of respiratory complications. Mitral valve operations produced fewer respiratory complications than multiple valve operations, but more than aortic valve operations. The duration of operation appeared to be more important than the duration of perfusion in relation to the development or respiratory complications in all groups. Age at operation was important only in the group with congenital disease. Of 12 patients less than nine years of age, five had respiratory complications, and four of these were severe.

There was no relationship between the severity of the pulmonary complications and the maximum concentration of free haemoglobin in the plasma postoperatively. There was no relationship between the degree of hypothermia and the incidence of respiratory complications.

This study demonstrates the multiplicity of factors which may influence the respiratory course after CPBP. These factors must be considered in comparing studies of post-bypass pulmonary physiology.

3. Pulmonary physiology changes following cardiopulmonary bypass

a) Pulmonary blood-gas exchange

There are several studies of changes in respiratory function soon after CPBP.

Andersen et al. (1970) investigated 30 bypass and 30 non-bypass procedures. The CPBP patients had anteromedial thoracotomies with opening of the pleura. The disc oxygenator and hypothermia were used. The non-bypass group had mainly orthopaedic operations. Pulmonary total flow resistance, total static compliance, ΔAaP_{O2} and V_D/V_T were measured during anaesthesia, and before opening and after closure of the chest, in the CPBP group.

Pulmonary function appeared to deteriorate during CPBP, but not during other surgical procedures. Total flow resistance and ΔAaP_{O2} increased about 20 to 25%. Total static compliance decreased 10% during CPBP. V_D/V_T was unchanged by CPBP. The CPBP and non-bypass groups were however, quite different in respect of preoperative lung function. The non-bypass group had preoperative lung function tests as follows: total flow resistance = 4.6 cm $H_2O.l.^{-1}.s^{-1}$; total static compliance = 57.4 ml.cm H_2O^{-1}; ΔAaP_{O_2} = 215 mm Hg. Corresponding values for the CPBP group were 7.3, 48.2 and 275. Seventeen of the cardiac patients were in class III or IV of the New York Heart Association classification.

A close relationship was found between the results of pulmonary function tests preoperatively and the cardiac status preoperatively. This correlation was reflected in all of the measurements except ΔAaP_{O_2}.

The authors conclude that pulmonary function deteriorated during cardiopulmonary bypass, while non-bypass procedures had no

pulmonary effect. While this may apply to the groups described it can not be taken as a general rule. The differences might not have appeared if the groups had been matched according to preoperative lung function. Also orthopaedic procedures are likely to have considerably less effect on the lungs than thoracotomy especially when, in the latter, the pleura was opened. Thus no definite conclusions about the specific effects of CPBP on pulmonary function can be reached from this study.

Norlander et al. (1969) studied early changes following CPBP. They described changes in oxygen uptake, cardiac output, physiological dead space and venous admixture in a mixed group of patients undergoing open heart surgery. CPBP was accomplished with a disc oxygenator and moderate haemodilution (25-30%) and hypothemia (30 - 32°C). Measurements were made at the following times:

(1) during anaesthesia and controlled ventilation with the chest closed

(2) with the chest open (median sternotomy)

(3) five min after the end of CPBP, with the chest still open

(4) at the end of the operation with the chest closed but the patient still anaesthetised.

'Mixed venous blood' was obtained from a catheter in the right atrium. Inspired O_2 concentration was measured with a paramagnetic analyser and the patients were ventilated with either 100% O_2 or a 50/50 mixture of nitrous oxide and O_2. The results are summarised in Table 9.

The authors discussed the significance of the oxygen saturation of mixed venous blood in determining ΔAaP_{O_2}. This was

Table 9.

Norlander et al. (1969)

Time	$\dot{V}_{O_2}$ ($ml.min^{-1}.m^{-2}$)	ΔAaP_{O_2} (mm Hg)	$\Delta a\bar{v}C_{O_2}$ ($ml.l^{-1}$)	Cardiac index ($l.min^{-1}.m^{-2}$)	$\dot{Q}va/\dot{Q}t$%	V_D/V_T%	Compliance ($l.cmH_2O$)
1.	114	349				52.4	0.037
2.	115	343	47.8	2.59	19.9	56.0	0.044
3.	123	361	45.4	2.64	20.0	53.1	0.047
4.	130	398	60.8	2.11	18.6	51.6	0.036
	period 1-4	period 1-4	period 2-4	period 2-4	period 2-4	period 1-4	period 1-4
	2P<0.01	2P<0.05	2P<0.01	2P<0.40	-2P<0.70	2P<0.30	2P>0.5
							period 1-3
							2P<0.02

Nordén et al. (1970)

1.	121	362	44	3.25	24	48	0.032
2.	126	380	48	3.02	20	49	0.039
3.	128	439	46	3.11	23	47	0.037
4.	151	370	53	3.25	18	48	0.027
	period 1-4						period 1-4
	2P<0.001						2P<0.001

most important at the end of the operation when the lowest cardiac outputs were present. They point out that if $\Delta\bar{a}vC_{O_2}$ had been assumed rather than measured, then shunting would have appeared more impressive and perhaps have led to erroneous conclusions as to the presence of widespread atelectases of the lungs.

In a similar study from the same department, Norden et al. (1970) confirmed most of these findings. The later study was done to assess the effects of certain changes in anaesthetic technique which had been introduced since Norlander et al.'s report in 1969. Lower halothane concentrations were used and fentanyl used for abolition of pain. An improved heart-lung machine had been introduced. Differences between the patients makes comparison of the 1969 and 1970 studies difficult, although the mean ΔAaP_{O_2} of both groups in period 1 were similar. In the 1970 study Norden et al. found that cardiac output fell less by the end of operation than it had done in the 1969 study although this may in part be due to different oxygen uptakes; $\Delta\bar{a}vC_{O_2}$ at the end of the operation still rose. These results are shown in Table 9.

It is not clear whether the apparent differences in cardiac output at the end of operation between the two studies is due to halothane's depressive effects on the myocardium or is related to the different preoperative cardiac indices. Again no significant changes in V_D/V_T ratio or venous admixture between the various periods were found. A decrease in compliance occurred in period 4. In two patients the decrease was probably related to left-heart failure. The fall in compliance was not associated with an increase in ΔAaP_{O_2} nor an increase in venous admixture.

It seems from these studies that cardiopulmonary bypass

has little immediate effect on pulmonary blood-gas exchange. The fall in PaO_2 and rise in ΔAaP_{O_2} may be due mainly to an increased $\Delta a\bar{v}C_{O_2}$ and increased $\dot{V}O_2$. Pulmonary compliance may fall a little at the end of bypass.

Studies later in the post-operative period

Tables 10, 11, and 12 show values obtained for PaO_2, $\dot{Q}va/\dot{Q}t$ and ΔAaP_{O_2} in 7 studies. For $\dot{Q}va/\dot{Q}t$ and ΔAaP_{O_2} the results are also expressed as percentage change from the pre-operative value. The most obvious feature of these results is their wide variation and the reasons for these differences merit discussion. McClenahan et al. (1965) studied two groups of patients. Group I consisted of eight patients (mean age 27 yr) who had cardiac operations with CPBP. Group II comprised six subjects (mean age 22 yr) who had intrathoracic procedures without CPBP. All patients had normal lung function preoperatively as defined by $\Delta AaPO_2$ and $\dot{Q}va/\dot{Q}t$. Group I had median sternotomies and bypass with a disc oxygenator, hypothermia (30°C) and homologous blood prime.

The main fault of McClenahan's method is his calculation of venous admixture. Oxygen capacity was assumed to be 20 vol % unless the packed cell volume was below 40% or above 50%. In these circumstances the capacity was taken as Hb (g per 100 ml) x 1.34. When calculating CaO_2 the arterial oxygen tension and pH were used to read the percentage oxygen saturation from the dissociation curve and then CaO_2 = capacity x $SaO_2/100$ + PaO_2 x .003
With the frequent alterations in haemoglobin concentration post-operatively, his assumption of oxygen capacity is likely to have been inaccurate.

McClenahan's failure to sample mixed-venous blood and his

Table 10. Arterial oxygen tension before and after cardiopulmonary bypass.

Reference	Preoperative	Postoperative 2-3 hr	24 hr	48 hr	72 hr	160-190 hr	2-3 weeks
Air Breathing							
Turnbull et al. (1974)	91.5(2.79)		70.5(2.56)	71.8(2.65)	70.4(2.06)	73.7(1.60)	
Eltringham et al. (1968)	77.0(10.8)		60.5(7.9)	60.4(9.6)	63.1(11.8)	66.2(12.7)	78.8(10.1)
McClenahan et al. (1965)	105	70	65				103
Philbin et al. (1970)	84.8(13.5)	59.5(10.9)	58.2(8.7)	55.0(12.2)			
Fordham (1965)	87(10.5)	64(11.0)	56(10.1)	57(6.8)	62(6.7)	67(7.3)	
Hedley-Whyte et al. (1965) (a)Aortic			65(10.3)				
(b)Mitral			53(7.6)				
Oxygen Breathing							
Turnbull et al. (1974)	510(17.6)		276(24.6)		331(23.8)	413(14.9)	
Eltringham et al. (1968)	585(31)		447(105)	476(62)	492(60)	526(37)	596(29)
Geha et al. (1966) (a)Mitral	417	293	311	254			352
(b)Aortic	413	319	275	217			350
McClenahan et al. (1965)	605	440	350				580
Hedley-White et al. (1965) (a)Aortic			319(116)				
(b)Mitral			324(133)				

All values are means, with one standard deviation in brackets.

Table 11. Percentage venous admixture ($\dot{Q}va/\dot{Q}t\%$) before and after cardiopulmonary bypass.

Reference		Preoperative	Postoperative 2-3 hr	24 hr	48 hr	72 hr	160-190 hr	2-3 weeks
Air Breathing								
Hedley-Whyte et al.* (1965)	(a)Aortic	0.65		1.65				
	% Change	-		+154				
	(b)Mitral	1.40		2.65				
	% Change	-		+89				
McClenahan et al.(1965) ($\Delta a\bar{v}C_{O_2}$ assumed)		2.8	21.4	21.1	23.8			3.6
	%Change	-	+664	+654	+750			+29
Fordham (1965)		-	16.5(5.0)	23.5(10.6)	28.2(7.0)	25.2(4.7)		
Philbin et al. (1970)		5.3(3.4)	18.1(13.1)	19.7(10.0)	17.1(9.3)			
	% Change	-	+242	+272	+223			
Oxygen Breathing								
Eltringham et al.(1968)		4.75(2.9)		9.1(4.8)	8.5(2.8)	8.6(2.8)	7.7(2.0)	4.7(1.5)
	% Change	-		+92	+79	+81	+62	-1
McClenahan et al.(1965) ($\Delta a\bar{v}C_{O_2}$ assumed)		4.4	12.0	16.2	19.3			
	% Change	-	+173	+268	+339			
Philbin et al. (1970)		3.85(5.3)	13.43(10.1)	8.9(4.8)	9.1(4.2)			
	% Change	-	+249	+131	+136			

$$\% \text{ Change} = \frac{\text{Postoperative value - preoperative value}}{\text{Preoperative value}} \times 100$$

* = These values are for O_2 capacity - arterial O_2 content (ml/100 ml).

All values are means with one standard deviation in brackets.

Table 12. ΔAaP_{O_2} before and after cardiopulmonary bypass.

Reference		Preoperative	Postoperative 2-3 hr	24 hr	48 hr	72 hr	160-190 hr	2-3 weeks
Air Breathing								
Turnbull et al. (1974)		12.7(3.68)		40.2(2.58)		38.5(2.20)	25.9(3.08)	
	% Change	-		+216		+203	+104	
Eltringham et al.(1968)		27.6(11.3)		40.5(12.4)	43.4(11.1)	44.2(11)	38.2(12.5)	24.8(10.5)
	% Change	-		+47	+57	+60	+38	-10
McClenahan et al.(1965)		8	33	36	40			?
	% Change	-	+313	+350	+400			-13
Fordham (1965)		15(9.5)	37(14.6)	48(11.1)	52(8.1)	49(9.5)	35(9.1)	
	% Change	-	+147	+220	+247	+227	+133	
Philbin et al. (1970)		27.7(12.3)	55.2(13.1)	48.8(9.4)	56.2(9.1)			
	% Change	-	+99.3	+76.2	+103			
Oxygen Breathing								
Turnbull et al. (1974)		130(14.8)		359(19.9)		323(18.9)	188(16.9)	
	% Change	-		+176		+148	+45	
Eltringham et al.(1968)		87.5(29.0)		214(117)	194(66)	185(60)	142(35)	80.4(26)
	% Change	-		+145	+122	+111	+62	-8
Geha et al.(1965) (PAO_2 assumed = 635)	(a)Mitral	218	342	324	381			283
	% Change	-	+57	+49	+75			+30
	(b)Aortic	222	316	360	418			285
	% Change	-	+42	+62	+88			+28
McClenahan et al.(1965)		79	236	326	357			
	% Change	-	+199	+313	+352			

All values are means, with one standard deviation in brackets.

$$\% \text{ Change} = \frac{\text{Postoperative value - preoperative value}}{\text{Preoperative value}} \times 100$$

use of an assumed arteriovenous oxygen-content difference (50 ml. l^{-1}) is a much greater potential source of error. It seems probable that group I (all of whom had major intracardiac surgery) might have had rises in $\Delta a\bar{v}C_{O_2}$ postoperatively and therefore their calculated venous admixtures, would have been overestimated.

In the discussion of Part I page (59) the effect of error in the assumption of $\Delta a\bar{v}C_{O_2}$ upon the derived value of $\dot{Q}va/\dot{Q}t$ is estimated for a small venous admixture. The size of this error increases with the size of admixture. McClenahan et al. reported venous admixtures postoperatively of about 20% and representative calculations show that a 40% underestimation of $\Delta a\bar{v}C_{O_2}$ would cause an error in $\dot{Q}va/\dot{Q}t$ of +25%. Errors of this order are quite possible after open cardiac surgery, if the value for $\Delta a\bar{v}C_{O_2}$ is assumed to be 50 ml. l^{-1}.

McClenahan attempted to justify his assumption of constant arteriovenous O_2 content difference on the following grounds. Boyd et al. (1959) measured cardiac output in a group of patients who had a cardiac index greater than two litres per m^2 per minute and a pulmonary arterial saturation of more than 50% during the postoperative period; the average $\Delta a\bar{v}C_{O_2}$ on the day of operation and for the two days thereafter was 53, 50, and 50 ml l^{-1} respectively. Since McClenahan excluded all patients with "a doubtful or poor postoperative cardiovascular status" he felt justified in assuming no great changes in $\Delta a\bar{v}C_{O_2}$ in his group I. The results to be described later show that this assumption is quite untenable.

The accuracy of McClenahan's calculated venous admixtures is important. In comparing his two groups he concludes: "Patients who undergo cardiac surgery with extracorporeal circulation develop

significent alveolar-arterial oxygen-tension differences and venous admixture in the early postoperative period. The cardiopulmonary bypass procedure may be responsible for initiating the underlying pathology, since changes of similar magnitude were not found after cardiac operations in which bypass was not required".

Some of the comparative results on which this conclusion is based are shown in table 13. In the light of the foregoing discussion it is reasonable to suppose that some of the apparent gross changes in the venous admixture of group I is due to its overestimation in the postoperative period. In comparing the values of ΔAaP_{O_2}, the preoperative difference between the groups is a problem, especially as the air-breathing values of group II cannot be expressed as percentage change. It may not be valid to compare postoperative ΔAaP_{O_2} (even as percentage change from the preoperative values) between the two groups, because the preoperative values of ΔAaP_{O_2} were so different. The percentage change in ΔAaP_{O_2} during oxygen-breathing is not markedly different in the two groups. ΔAaP_{O_2} is a relatively poor indicator of pulmonary function in a group in whom mixed-venous oxygen content is almost certainly altering. Also, McClenahan's calculated venous admixture must often have been inaccurate. His conclusions are thus open to serious question.

Hedley-Whyte et al. (1965) studied 18 patients who underwent elective aortic or mitral valve operations. They were divided into three groups:

(a) aortic valve replacement with CPBP

(b) mitral valulotomy without CPBP and

(c) mitral valve surgery with CPBP.

Table 13. McClenahan et al. (1965)

	ΔAaP_{O2}									
	Preoperative		Postoperative							
			3 hr		24 hr		48 hr		Several Weeks	
	Air	100% O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2
Group I	8	79	33	236	36	326	40	357	7	-
% Change	-	-	+312	+199	+350	+313	+400	+352	-12.5	-
Group II	0	45	14	111	11	118	18	138	-	-
% Change	-	-	-	+147	-	+162	-	+207	-	-
	$\dot{Q}va/\dot{Q}t$ %									
Group I	2.8	4.4	21.4	12.0	21.1	16.2	23.8	19.3	3.6	-
% Change	-	-	+664	473	+654	+268	+750	+339	+28.6	-
Group II	0	3.6	8.0	6.0	5.5	6.5	9.7	-	-	-
% Change	-	-	-	+66.6	-	+80.6	-	-	-	-

$$\% \text{ Change} = \frac{\text{postoperative value} - \text{preoperative value}}{\text{preoperative value}} \times 100$$

Group I CPBP

Group II Non-CPBP

Cardiac outputs were measured by the Fick and dye methods. Simultaneous blood samples were obtained from the main pulmonary artery and radial artery. In the preoperative studies the only blood analyses made were for oxygen content and capacity. It is, therefore, not possible to compare pre- and postoperative venous admixtures. The results are summarised below.

	CARDIAC INDEX ($l.min^{-1}.m^{-2}$)		P.A. pressure (mmHg)	O_2 Capacity-CaO_2 (ml per 100 ml)		Post-op. $\dot{Q}va/\dot{Q}t$ (%)	
	Pre-op.	Post-op.	Pre-op.	Pre-op.	Post-op.	Air	O_2
(a)	2.0(.2)	2.8(.4)	18(4.0)	0.65	1.65	15	14
(b)	2.2(.3)	2.0(.3)	28(6.25)	0.65	1.5	15	12
(c)	2.0(.3)	2.0(.2)	38(6.0)	1.4	2.65	26	14

Mean values, with one standard error of the mean in brackets.

Breathing air, 24 hr after operation, mean values for PaO_2 were for group (a) 65, group (b) 67, and group (c) 53 mm Hg. Impairment of arterial oxygenation was increased after surgery. The only available comparison of pre- and postoperative values is as oxygen capacity minus arterial oxygen content. There was little change in oxygen-carrying capacity between these two periods.

The post-operative increase in the difference between oxygen capacity and arterial O_2 content was not correlated with changes in cardiac output, radiological evidence of atelectasis, pulmonary arterial hypertension or left atrial hypertension.

$\dot{V}O_2$ increased by an average of 20% after operation, consistent with the observed average increase in oral temperature of 1.2°C. Only in group (a) was the rise in cardiac index

appropriate to the change in $\dot{V}O_2$. Post-operative $\Delta a\bar{v}CO_2$ was increased (group (a) 58, group (b) 62, and group (c) 72 $ml.l^{-1}$).

Hedley-Whyte et al. (1965) concluded that there was no significant difference in the magnitude of shunts in the three groups studied, regardless of whether CPBP was used or not. They suggest that the degree of shunting and hypoxaemia is compatible with the effects of major surgery and that there is little contribution due specifically to the effects of CPBP.

Fordham (1965), working at the National Heart Hospital, London, described pulmonary blood-gas exchange following aortic valve operations with CPBP in 18 patients. Twelve of these had "no major postoperative complications" although all but one had radiological changes including several with lobar or segmental collapse. Many are described as having increased cough with sputum which was often purulent and copious after the operation.

In the preoperative tests only arterial blood was sampled but postoperatively pulmonary-artery or right-atrial blood was obtained as well, and thus venous admixture could be accurately calculated. In calculating alveolar oxygen-tension the respiratory exchange-ratio was assumed to be 0.76. Fordham's results are shown in Tables 10, 11, and 12. It is a pity that venous admixture was not measured preoperatively but assuming a haemoglobin of 15 g per 100 ml, temperature 37°C, $\Delta a\bar{v}CO_2$ 55 $ml.l^{-1}$ and using the given preoperative values for PAO_2 and PaO_2, preoperative $\dot{Q}Va/\dot{Q}t$ is calculated as 4.5%. This means the percentage increases in venous admixture on postoperative days 1 and 2 would be of the order of 400-500%, a finding similar to that of McClenahan et al. (1965).

Arterio-venous oxygen-content difference was not

measured preoperatively and changed little during the first three days postoperatively (2-3 hr, 57, 24 hr, 59, 48 hr, 52 $ml.l^{-1}$).

No correlation was found between the degree of hypoxaemia and the duration of bypass, or with plasma haemoglobin levels at the end of perfusion. Patients aged 30-39 yr were significantly less hypoxic on the second and third postoperative days than those 50-59 years of age.

Pulmonary blood-gas exchange showed a fairly constant pattern, becoming worse until the second postoperative day and then beginning to improve. $\Delta AaPO_2$ had not returned to the preoperative level at 7 days after operation. Fordham suggested that the changes were greater than those found in a series of 10 closed cardiac operations, without bypass. Mean $\Delta AaPO_2$ values, for the latter, on the evening of operation and on the following two days were 22, 24 and 26 mm Hg respectively. No other details about these patients are given. This compares with values of 37, 48 and 52 mm Hg for the bypass group. The conclusion about degree of change seems unjustified as the mean $\Delta AaPO_2$ for the non-bypass group preoperatively is not known.

An interesting observation made by Fordham was that when the hypoxaemia was at its most severe, the mean $PaCO_2$ values were decreased to 32-34 mm Hg. This hyperventilation did not appear to be a response to hypoxaemia, since raising the arterial oxygen content did not raise $PaCO_2$ significantly.

In comparing Fordham's results with the other studies listed it should be borne in mind that although his patients were stated to have had no major postoperative complications, many had radiological changes in the lungs accompanied by cough and sputum.

These would usually be considered abnormal.

Geha et al. (1966) measured PaO_2 in 23 patients following CPBP. Ten had mitral-valve replacement, six replacement of the aortic valve, four repair of atrial septal defect and three repair of tetralogy of Fallot. Results are shown only for the aortic and mitral groups (tables 10 and 12). The alveolar-arterial oxygen-tension gradient was highest about 48 hr after operation. $\Delta AaPO_2$ was sometimes still increased two weeks after operation. Geha et al. (1966) do not report values for $\Delta AaPO_2$ but give a mean calculated PAO_2 breathing oxygen and mean values for PaO_2 at the different time intervals. PAO_2 was calculated from the alveolar-air equation. The respiratory exchange-ratio determined after open-heart surgery in a previous study was used in the calculation ($R = 0.76-0.77$).

Eltringham et al. (1968) described pulmonary-function studies before and after correction of mitral insufficiency with CPBP in 12 patients aged 30 - 69 yr with pulmonary hypertension. Mixed venous blood was sampled directly in all the studies. Post-operatively all patients had assisted ventilation with an Emerson volume-regulated respirator with high respiratory pressures. Nine patients were ventilated for 8 hr, two patients for 24 hr, and one for 36 hr. Studies were made with the patients breathing spontaneously either air or 100% O_2. Cardiac output was determined by the dye-dilution method. PAO_2 on room air was calculated from the alveolar-air equation assuming R equal 0.86. On 100% O_2 PAO_2 was obtained by subtracting water-vapour pressure and arterial CO_2 tension from barometric pressure. $PaCO_2$ was assumed equal to $PACO_2$. A variation of R of ± 0.15 would cause an error in estimated PAO_2 of $\pm 5-8$ mm Hg.

The results are shown in the tables 10, 11, and 12. At 8-10 days after operation values for PaO_2 breathing air and O_2 had still not returned to the preoperative level, but had done so at the last study (mean 20 days).

On 10 occasions in 5 different subjects cardiac output was measured postoperatively after breathing air for 15 min and repeated after 15 min of O_2 breathing. Mean $\dot{Q}t$ when breathing air was 4.2 (SD 0.7)$1.min^{-1}$ and during O_2 breathing 3.9 (SD 0.7)$1.min^{-1}$. In 60 instances $\Delta a\bar{v}C_{O_2}$ was measured breathing air and after 15 min of breathing O_2. On air the mean value was 53.7 (SD 10.0) and on O_2 it was 60.1 (SD 10.0) $ml.1^{-1}$. This change was significant.

The large shunts during O_2-breathing led Eltringham et al. (1968) to conclude that atelectasis is an important factor in the production of hypoxaemia. They stated that even in the presence of these big shunts, the X-ray appearances were usually deceptively satisfactory.

The actual values for oxygen-breathing venous admixture and $\Delta AaPO_2$ were lower in this series than in McClenahans and Hedley-Whyte's studies. They were also lower than in a group of patients who underwent abdominal surgery (Diament and Palmer, 1967). Eltringham et al. (1968) thought that this was a strong argument against incriminating CPBP as a specific factor in the causation of post-operative pulmonary dysfunction. The routine use of assisted ventilation after operation in Eltringham's patients but not in any of the other studies makes this argument hard to accept.

Eltringham et al. (1968) concluded that factors common to all major surgery are more important than CPBP in producing atelectasis and hypoxaemia. Such factors include shallow breathing and failure

to take deep breaths. The arterial PO_2 returned to preoperative levels only when more vigorous activity was undertaken.

Turnbull et al. (1974) assessed pulmonary function ($\Delta AaPO_2$, DCO, V_D/V_T) in a group of 19 patients before and after CPBP. These patients were clinically free of chest disease or overt congestive cardiac failure except for one case of mitral and aortic valve replacement. Seventeen cases had coronary artery bypass grafts for angina pectoris. Bypass was achieved with a bubble oxygenator and homologous blood prime. The lungs were kept inflated and intermittent "sighs" were administered during bypass. All preoperative chest X-rays were normal except for the case mentioned.

Steady-state diffusing capacity (D_LCO) was measured by the Filley method. (Filley, MacIntosh and Wright, 1954). End-tidal O_2 and CO_2 concentrations corresponding to the blood sampling periods were assumed to equal alveolar concentrations. These values were used to calculate $\Delta AaPO_2$, and $\Delta aAPCO_2$. Arterial PCO_2 was substituted for $PACO_2$ in the Bohr equation for calculation of V_D/V_T ratio. Postoperative chest X-ray changes seem to have been pronounced. Fifteen patients were described as having lobar collapse at some stage after surgery (13 of these were left lower lobe).

Changes in PaO_2 and $\Delta AaPO_2$ are shown in tables 10 and 12. D_LCO values before, and at 1, 3 and 7 days after, operation were 17.7 (SD 0.86), 9.4 (SD 1.08), 13.7 (SD 1.46), 12.5 (SD 1.08) ml. min^{-1}. mm Hg^{-1} respectively. In individual patients PaO_2 was related to the duration of bypass and X-ray changes. Turnbull et al. (1974) suggested that the changes in D_LCO might be due to increased shunting, decrease in functioning lung volume or diffusion block.

V_D/V_T ratios were as follows: preoperatively, 0.37 (SD .05); 1 day, 0.388 (SD .04); 3 days, 0.439 (SD .05); 7 days, 0.460 (SD .03). Changes in $\Delta aAPCO_2$ were significant on the first postoperative day (1.8 mm Hg - 3.4 mm Hg).

Turnbull et al. (1974) speculated on refinements in bypass technique which might reduce complications. They suggested the use of blood and pump filters, omission of blood from the pump prime and suction of right and left lower lobe bronchi before extubation.

Philbin et al. (1970) in a study of 14 patients with acquired valvular disease made pre- and postoperative measurements of haemodynamics and respiratory gas-exchange. The patients all had median sternotomies and bypass with the bubble oxygenator. Post-operative measurements were made immediately while still on assisted ventilation and on the first and second days with the patients breathing spontaneously. Mixed-venous blood was sampled directly from the pulmonary artery.

The results are shown in tables 10, 11 and 12.

b) Pulmonary ventilation and mechanics

McClenahan et al. (1965) studied the change in ventilatory pattern following surgery in both CPBP and non-bypass groups. In both groups frequency (f) increased immediately after operation and had doubled by the 2nd postoperative day. In several cases f was still raised one week after operation. Tidal volume (V_T) fell dramatically and was still reduced several weeks after operation. The fall appeared to be greater in the bypass group.

Howatt et al. (1962) measured lung volumes before and after CPBP in 11 patients. Functional residual capacity was measured by the open-circuit nitrogen-washout method. On the first post-operative day there was a large decrease in vital capacity and a similar decrease in inspiratory and expiratory reserve volumes. Functional residual capacity fell to about 50-70% of the preoperative value 1 day after operation. Residual volume increased a little. Respiratory frequency nearly doubled and tidal volume was halved. By the eigth day the lung volumes had almost returned to the preoperative levels.

Osborn et al. (1962) found no change in pulmonary compliance in a large group of patients during the period immediately following CPBP. Sullivan et al. (1966) also showed that dynamic compliance of the total respiratory system, elastic work and resistive work were unchanged 30 min after CPBP. $\dot{Q}va/\dot{Q}t$ during O_2-breathing was also unchanged at this time. Studies of the same mechanical indices before sternotomy and after closure of the chest showed no significant differences. Thus it appears that CPBP itself causes no immediate deterioration in pulmonary mechanics.

4. Changes in cardiac output following cardiopulmonary bypass

Kirklin and Theye (1963) measured cardiac output in 47 patients after open-heart surgery. On postoperative days 1, 2 and 3, cardiac index averaged 3.2, 2.7 and 2.9 $l.min^{-1}.m^{-2}$ respectively. The authors discuss factors affecting cardiac performance after operation. These include, the nature of the original anatomical lesion and the details of the operative procedure. Ventriculotomy is probably the most important factor. Other significant factors include, ventricular-outflow resistance (patients with elevation of pulmonary arterial pressure secondary to pulmonary vascular disease had lower postoperative cardiac outputs) and blood transfusion. No consistent change in cardiac output was noted when an O_2-rich inspired gas was changed to room air. Similarly no consistent change was found on changing from intermittent positive-pressure ventilation to spontaneous breathing. The effects of digitalis in the postoperative period were variable. Many of the patients were in sinus rhythm.

In discussing the criteria of an adequate postoperative cardiac output Kirklin and Theye (1963) suggested the oxygen saturation of mixed-venous blood should best reflect tissue oxygenation. They point out that the mixed-venous saturation depends on arterial oxygen-content and the metabolic rate as well as cardiac output. Harris, Seelye and Barratt-Boyes (1974) showed, however, that such an interpretation of $\Delta a\bar{v}C_{O_2}$ may be fallacious, in the presence of peripheral systemic arterio-venous shunting.

Kirklin and Theye indicate ways in which the depression of myocardial function might be minimised. These include use of transverse ventriculotomy, prevention of coronary air embolism,

and protection of the myocardium by cooling during ischaemia. Minimal use of homologous blood for priming the pump and minimising metabolic acidosis are also likely to help cardiac function after surgery.

A comparison of cardiac output and stroke volume at various atrial pressures after repair of atrial septal defect by a variety of techniques gave only equivocal evidence that normothermic CPBP impaired ventricular function.

Yashar et al. (1971) measured blood volume and cardiac output in 50 patients before and after open-heart procedures for various congenital and acquired cardiac lesions. Bypass was performed with a bubble oxygenator and bloodless prime. Blood volume was measured by a tracer dilution technique using radioactive-iodine-tagged albumin. Cardiac output was measured by dye dilution in 20 patients before operation, within 24 hrs afterwards and again at 7 to 10 days. The preoperative cardiac index for the entire group was below normal (mean 1.27 $l.min.^{-1}m^{-2}$). Within 24 hrs it increased to normal values (mean 2.72 $l.min^{-1}m^{-2}$). No significant change occurred at 10 days (mean 2.82 $l.min^{-1}m^{-2}$).

There was a mean fall in blood volume of 21.5% in the immediate postoperative period and since this was not reflected in blood loss or changes in body weight Yashar et al. (1971) suggested that it represented the redistribution of fluid. Blood volume was restored to the preoperative level at 8 to 10 days. Many of these patients had aortic or mitral stenosis and low preoperative cardiac outputs. The postoperative increase in cardiac output was thus probably due to correction of the anatomical lesion.

Hedley-Whyte et al. (1965) found that the cardiac output

at 24 hr after operation was slightly low in relation to the increased oxygen uptake.

Philbin et al. (1970) found a mean preoperative cardiac index (measured by dye dilution) of 2.41 (SD 0.18) $1.min^{-1}.m^{-2}$. On the day of operation (artificial ventilation), day 1 and day 2 it was 2.2 (SD 0.15), 2.2 (SD 0.18) and 2.55 (SD 2.3) $1.min^{-1}.m^{-2}$ respectively. Philbin et al. (1970) demonstrated the contribution of reduced cardiac output to arterial hypoxaemia in the postoperative period.

This confirmed a theoretical paper of Kelman et al. (1967) which described the possible effects of a change in cardiac output on arterial PO_2 when venous admixture was present. These workers explored the theoretical relationship between cardiac output, venous admixture and $\Delta AaPO_2$ and concluded that the previously noted reductions in PaO_2 after anaesthesia might be caused largely by reductions of cardiac output. When allowance was made for these it appeared that the venous admixture during anaesthesia might not be greatly increased above normal. Kelman et al. (1967) point out that in the absence of venous admixutre PAO_2 is equal to PaO_2 and depends on $\dot{V}A$, $\dot{V}O_2$ and FIO_2. If venous admixture is present PaO_2 becomes dependent on cardiac output and CaO_2 as well.

There is little information about the changes in cardiac output that follow coronary artery surgery. With normal cardiac output before operation, normal pulmonary vascular resistance, no ventriculotomy and use of hypothermia one might expect little deterioration in cardiac function.

5. Pulmonary physiological changes following major surgery without bypass

a. Ventilatory pattern and lung volumes

Zikria et al. (1974) used a canopy-computer-spirometry system to record, breath by breath, lung volume changes for periods of up to 75 min. They studied ventilatory pattern in normal subjects and pre- and postoperative patterns in patients having inguinal herniorrhaphy or upper abdominal surgery.

The normal subjects and the preoperative patients showed oscillations of tidal volume and end expiratory level. Tidal volume and expiratory baseline appeared to oscillate in phase and Zikria suggested that a big tidal volume coinciding with a high end-expiratory position has the effect of a sigh on alveolar inflation.

After upper abdominal operations there was a 20% decrease in tidal volume and a 47% increase in respiratory frequency. There was no significant change after inguinal herniorrhaphy.

Since a test 'run' usually comprised 500 to 1500 breaths it was possible to obtain estimates of the distribution of tidal volumes. For normal subjects the tidal-volume distribution is stable from day to day. Inguinal herniorrhaphy had no significant effect on the distribution curves. Upper abdominal operations reduced the mean tidal volume, narrowed the distribution, markedly decreased the incidence of larger-than-normal breaths and abolished sighing. Following upper abdominal operations the fraction of breaths with tidal volume greater than 110% of the preoperative mean decreased from 33% to 10% and breaths greater than 200-300% of V_T were abolished. Sighing (300% V_T) occured in 1% of all breaths among a series of Bendixen et al. (1964) and in 0.3% of normal in Zikria's study.

Zikria et al. (1974) concluded that incisional pain and muscle spasm together with restricted diaphragmatic movement led to the rapid, restricted type of breathing seen after upper abdominal operations. Absence of sighing and large breaths, as well as diminution of tidal volume and reduced oscillations of end expiratory position, might produce incomplete inflation and microatelectasis.

It is reasonable to assume that the pulmonary effects of anaesthesia, incisional pain, sedation, difficulty in coughing and immobility after upper abdominal operations are similar to their effects following cardiac surgery with sternotomy. This review of the effects of surgery on pulmonary physiology will therefore refer mainly to the influence of upper abdominal operations. Major differences might than tentatively be attributed to cardiopulmonary bypass.

Latimer et al. (1971) showed in 46 patients having elective upper abdominal operations that impairment seen on preoperative pulmonary function (FEV, and FVC) studies increased the rate of clinical pulmonary complications as did obesity, smoking and prolonged anaesthesic time.

Anscombe et al. (1958) measured functional residual capacity and vital capacity in three groups of patients. Group I consisted of 10 control patients none of whom had a condition likely to affect the respiratory system and none of whom underwent an operation. Group II contained 13 patients, six of whom had upper abdominal operations and seven of whom had inguinal herniorrhaphy. Group III contained 3 patients who had surgery on a limb. Measurements were made twice in each subject, 24 hr before and 48 hr after operation in Group II and III. The subjects were recumbent for the measurements

and FRC was measured by a helium equilibration method. Results were as follows:

	Group I		Group II		Group III	
	1st	2nd	Preoperative	Postoperative	Preoperative	Postoperative
FRC	3.3	3.4	3.8	3.2	3.2	3.0
ERV	0.8	0.7	0.9	0.6	0.8	0.8
VC	3.7	3.8	4.1	2.9	4.0	4.2
RV	2.5	2.7	2.9	2.6	2.4	2.2
TLC	6.2	6.4	7.1	5.5	6.4	6.3
IRV	2.9	3.0	3.2	2.3	3.2	3.4

Changes in lung volumes were greater in those of group II who had upper abdominal operations than in those who had inguinal herniorrhaphy e.g. FRC 4.0 to 3.2 l. for upper abdominal operations as compared with 3.5 to 3.2 l., and VC 4.4 to 2.4 l. as compared with 4.0 to 3.5 l.

Alexander et al. (1973) described similar changes in lung volumes following upper abdominal operations. FRC fell to 70, 79 and 93% of the preoperative value on the 1st, 2nd and 5th day respectively after vagotomy and pyloroplasty. FRC was measured by the closed circuit nitrogen equilibration technique. Chest splinting due to wound pain and abdominal and thoracic muscle spasm were thought to have shifted the balance of lung forces to a lower lung volume at FRC. Obese patients, having a reduced FRC to start with, deteriorate further. These authors suggested that the reduction in FRC following thoracotomy may be less than following upper abdominal operations since, in the latter, distention of abdominal viscera and raising of the diaphragm adds to the problem.

Alexander et al. (1973) concluded that the main significance of the postoperative fall in FRC is the invasion of the tidal breathing range by significant airway closure. They have demonstrated how this mechanism may be responsible for postoperative hypoxaemia. In 67 patients, they measured closing volume, FRC, PaO_2 and $\Delta AaPO_2$, before and after upper abdominal surgery. CV was little changed by the operation. Regression of $\Delta AaPO_2$ on (FRC - CC) gave a highly significant correlation ($r = -0.61$). FRC - CC has a negative sign when airways close within the tidal breathing range. The mean values for FRC - CC were: preoperatively +0.38, 1 day postoperatively -0.03, 2 days postoperatively 0.00, 5 days postoperatively +0.35.

The change in $\Delta AaPO_2$ after upper abdominal surgery was also correlated with the concomitant percentage reduction in FRC ($r = 0.503$, $P < 0.001$). Although no definite conclusions can be drawn from these statistical correlations it seems highly probable that the reduction of breathing level and subsequent increase in airway closure is in part responsible for increased venous admixture and arterial hypoxaemia following surgery. Airways closed throughout the respiratory cycle would contribute to venous admixture when oxygen was breathed and those cyclically open would produce a spectrum of reduced $\dot{V}/\dot{Q}$ ratios.

b. Blood-gas exchange

Table 14 lists values obtained from the literature for changes in PaO_2, $\Delta AaPO_2$ and $\dot{Q}va/\dot{Q}t$ after upper abdominal operations.

Gordh et al. (1958) studied 3 groups of patients classified by the method of anaesthesia used, namely (a) barbiturate nitrous oxide anaesthesia with succinylcholine, (BNS) (b) ether anaesthesia and (c) spinal anaesthesia.

Table 14. Arterial oxygen tension, $\Delta AaPO_2$ and $\dot{Q}va/\dot{Q}t$ before and after upper abdominal surgery.

Reference	No. of patients	Mean Age	Before Operation	Days after operation 1	2	3	4	5+
Air Breathing								
Gordh et al. (1958) (a)	14	-	80.6(11.3)	70.8(15.9)				
(b)	5	-	88.6(17.3)	76.6(14.7)				
(c)	7	-	82.4(21.1)	75.0(16.9)				
Palmer and Gardiner(1964)(a)	14	48	89.3	76.5	74.6	79.9	73.3	76.7
(b)	18	46	90.1	66.6	63.3	67.1	71.0	73.0
Diament and Palmer(1966)	64	52	92.4(13.3)	73.8(10.9)				
Knudsen (1970)(a)	8	67	89.3(8.8)	78.9(13.4)		74.4(7.3)		87.8(7.5)
(b)	8	61	91 (6.6)	78.2(5.6)		73.5(5.5)		79.1(5.1)
Alexander and Spence (1973)	101	43	86.3(9.25)	69.9(10.3)	71.0(11.7)			82.2(11.1)
Siler et al.(1974)	20	46	83 (8.9)	72 (13.4)		77 (13.4)		80 (8.9)
Air Breathing $\Delta AaPO_2$ Measurements before and after upper abdominal surgery								
Alexander and Spence (1973)	101	43	17.3(9.5)	32.7(11.1)	31.9(12.1)			21.9(12.1)
Siler et al.(1974)	20	46	23(13.4)	32(8.9)		30(13.4)		29 (13.4)
$\Delta AaPO_2$ Breathing Oxygen								
Gordh et al. (1958) (a)	14	-	150(88.5)	302(204)				
(b)	5	-	139(84.1)	223(119)				
(c)	7	-	133(81.6)	222(73.7)				
Venous admixture before and after upper abdominal surgery								
Air Breathing								
Diament & Palmer (1966 & 1967)	64	52	3.1	15.1				
Oxygen Breathing								
Diament & Palmer (1966 & 1967)	23	49.6	8.2	20.2				
Gordh et al. (1958)	19	-	10	19				

All values are means, with one standard deviation in brackets.

The authors calculated venous admixture for O_2-breathing assuming $\Delta a\bar{v}C_{O_2}$ to be 40 $ml.l^{-1}$. Patients who did not have upper abdominal operations have been excluded from the results.

Gordh et al. (1958) concluded that, during O_2-breathing 24 hr after operation, the low oxygen tensions indicated the presence of shunts, probably due to pulmonary atelectasis.

Palmer and Gardiner (1964) studied 32 patients before and after partial gastrectomy. Arterial oxygen saturation was measured and arterial oxygen tension was derived from the dissociation curves of Dill and Forbes (1941). These patients fell into two groups: (a) normal or uncomplicated, including 7 smokers and 3 bronchitics; (b) a complicated group who developed clinical and radiological evidence of atelectasis, including 14 smokers and 12 bronchitics.

Table 14 shows that in these patients significant hypoxaemia persisted for at least 5 days after the operation, and that this was most severe in patients with atelectasis. Alveolar hypoventilation could be excluded because arterial PCO_2 was slightly reduced, and the authors concluded that regional underventilation, and shunt past areas of atelectasis, were the causes of the hypoxaemia.

Diament and Palmer (1966) investigated the effect of (a) upper abdominal, (b) lower abdominal, and (c) non-abdominal operations on PaO_2 after operation. PaO_2 was read directly using a Radiometer electrode. The results for group (a) only are shown in table 14. The mean falls in PaO_2 after 24 hrs were 18.6 (SD 11.6), 9.5 (SD 10.0), 5.7 (SD 10.8) mm Hg in groups (a), (b) and (c) respectively.

Diament and Palmer (1967) reported a further study of postoperative hypoxaemia. They assumed that venous admixture breathing 100% O_2 was true shunt and that the difference between

this and air-breathing admixture would indicate the contribution of areas of low ventilation/perfusion ratio to arterial hypoxaemia. PaO_2 was measured in 23 patients while breathing 100% O_2 before and 24 hr after operation. Mean PaO_2 before the operation was 540 (SD 137) mm Hg and afterwards 360 (SD 155) mm Hg. The postoperative fall in PaO_2 was related well to radiological change.

From the increase in $\Delta AaPO_2$ of 180 mm Hg on the first postoperative day, and assuming a $\Delta a\bar{v}C_{O2}$ of 45 ml. l^{-1} the authors calculated that before operation "true shunt" ($\dot{Q}s/\dot{Q}t$) was 8.2% and afterwards 20.2%. Using the PaO_2 air-breathing values obtained from their 1966 patients and the same venous admixture calculation, air-breathing venous admixture before operation was 3.1% and afterwards 15.1%. Both these increases are in the region of 12%, and Diament and Palmer (1967) concluded that "true shunt" and not ventilation/perfusion imbalance accounted for nearly all the additional venous admixture effect in their patients, after operation.

Knudsen (1970) measured PaO_2 before and after operation in two groups of patients breathing air. Group (a) had upper abdominal operations for disease of the stomach. Group (b) had thoraco-abdominal operations for disease of the stomach or oesophagus. There were 8 patients in each group, and all had an entirely uncomplicated postoperative course. In the patients with abdominal incisions, PaO_2 was lowest on the 3rd day after operation, and in group (b) PaO_2 was lowest at day 4 or 5. Ten to 15 days after operation the PaO_2 in group (b) patients had still not returned to normal. The more pronounced and longer-lasting hypoxaemia in group (b) patients is probably not only due to the fact that the thoracic wall was involved but also because the surgical procedures were more extensive,

thus restraining diaphragmatic movement more severely.

The study of Alexander et al. (1973) has already been discussed. Their close correlations between $\Delta AaPO_2$ and (FRC - CC), and between postoperative change in FRC and postoperative change in $\Delta AaPO_2$, provide strong evidence that the reduction in breathing level and consequent airway closure is an important cause of the increase in postoperative venous admixture. Of the 101 patients in this study who had upper abdominal operations the majority had vagotomy and drainage and some had cholecystectomy. For the calculation of PAO_2, respiratory quotient was assumed to be 0.8. Arterial PO_2 was lowest 1 day after operation and had not returned to normal by the 5th postoperative day. The clinical postoperative course of these patients is not described.

Siler et al. (1974) measured $\Delta AaPO_2$ in 20 patients breathing air and oxygen before and after upper abdominal operations. They assumed R equal 0.8 in calculating PAO_2. Calculating venous admixture on oxygen using an assumed value for $\Delta a\bar{v}CO_2$, and assuming that this represented true shunt, they worked out the relative contributions of true shunt and abnormal ventilation/perfusion ratios to the air breathing $\Delta AaPO_2$. The authors concluded that air-breathing $\Delta AaPO_2$ was significantly increased on the 1st, 3rd and 6th days after operation and that the major contribution to this increase was from "shunt" as opposed to low $\dot{V}/\dot{Q}$ areas.

It does seem that much of the addition to venous admixture that follows major operations is not reversed by O_2-breathing. Venous admixture on O_2 is likely to include contributions from regions of complete atelectasis and from regions of critically low $\dot{V}/\dot{Q}$ ratio which are ventilated on air but close on O_2 breathing.

A paper by Colgan and Mahoney (1969) pointed, again, to the importance of measuring $\Delta a\bar{v}C_{O_2}$ directly when calculating venous admixture in patients after operation. Twelve patients, many of whom were "seriously ill", were studied before and after upper abdominal operations. Measurements were made of FRC, $\dot{Q}t$ and $\Delta a\bar{v}C_{O_2}$ and the effects of changes in these indices on the estimated shunt was explored. Measurements were made 1 hr after premedication in the operating room and again 1-4 hr after operation, with the patients breathing spontaneously. The time of the postoperative study depended on when the patient was able to cooperate sufficiently. Mixed-venous blood was sampled from a catheter in the right ventricle and air-breathing and O_2-breathing studies were made. Oxygen content was estimated from pH, PO_2, temperature and Hb, using the Severinghaus calculator. Content was also measured directly using a polarographic technique.

FRC changed little immediately following operation. No significant changes in air- or O_2-breathing admixture occurred either (cf. Norlander and Norden 1969, 1970 - early changes following CPBP). Before operation the mean $\dot{Q}t$ was 6 $1.min^{-1}$ and afterwards 4.8 $1.min^{-1}$ ($P < 0.025$). $\dot{V}O_2$ was unchanged.

The effect of using an assumed $\Delta a\bar{v}C_{O_2}$ of 45 $ml.l^{-1}$ and the actual measured $\Delta a\bar{v}C_{O_2}$ in calculating venous admixture was determined. In only 4 of the 12 patients were the actual and assumed values for venous admixture within 10% of each other. Errors in estimation of venous admixture could have been as large as 50% in some cases.

The mean values of $C\bar{v}O_2$ determined directly was 139 $ml.l^{-1}$ and 143 $ml.l^{-1}$ using the Severinghaus calculator. When calculating

content differences i.e. ($C\bar{c}O_2$ - CaO_2) and ($C\bar{c}O_2$ - $C\bar{v}O_2$) greater accuracy is likely to be achieved if both values are determined by the same method.

The authors point out that changes in PaO_2 or $\Delta AaPO_2$ are frequently interpreted as indicating changes in intrapulmonary shunt. An example from this paper shows how reductions in cardiac output alone may account for increases in $\Delta AaPO_2$ without changes in the underlying admixture. In a patient with 20% $\dot{Q}va/\dot{Q}t$, $\Delta AaPO_2$ could increase from 310 to 550 mm Hg if $\Delta a\bar{v}C_{O_2}$ increased from 40 to 70 $ml.l^{-1}$. Had $\Delta a\bar{v}C_{O_2}$ been assumed constant, the admixture would have been calculated at 30%.

6. Pulmonary and cardiac physiological changes due to propranolol

All the patients in the study to be described were taking a β-adrenergic blocking drug (usually propranolol) until 24 hr or less before operation. The results of the preoperative studies and studies soon after operation might therefore have been influenced by the effects of β-adrenergic blockade, and it is important to consider what these effects might have been.

Reports of the exacerbation of coronary ischaemic events after abrupt ending of β-blockade, supported by clinical experience at Green Lane Hospital, made it seem unreasonable to stop the study-group's propranolol earlier than normal. Miller et al. (1975) evaluated the effects on anginal symptoms of sudden withdrawal of large doses of propranolol (160-320 mg/day) or of placebo in 20 patients in a double-blind cross-over trial. Within 2 weeks of stopping propranolol, serious ischaemic events occured in 10 patients. Three had unstable angina, 1 had ventricular tachycardia, 1 had a fatal myocardial infarction and 1 died suddenly (cause not certain). The rebound phenomenon was related to the severity of angina before propranolol was given and also to the degree of relief of pain that the propranolol had produced.

Coltart et al. (1975) assessed the time necessary for the dissipation of radioactivity of labelled propranolol (^{14}C-) and its cardiac effects in the hearts of patients undergoing open-heart operations. The propranolol was given intravenously and orally. In one group of patients atrial tissue was examined for pharmacological activity by in-vitro isoprenaline challenge. The patients were divided into two groups: (a) 4 patients having coronary artery bypass surgery who had not received propranolol, and (b) 4 patients

in whom chronic propranolol treatment had been discontinued for 24 to 72 hrs before operation. There was neither chemically measurable propranolol nor evidence of pharmacological activity in patients of either group (a) or (b) at the time of operation. After the infusion of either 25 or 75 μCi of ^{14}C - labelled propranolol, the myocardial tissue concentration had declined to insignificant levels between 24 and 28 hours.

Levenson et al. (1974) studied nine normal volunteers who took increasing dose of propranolol to 800 mg/day. Haemodynamic effects were assessed by echocardiographic volume measurements, heart rate and blood pressure. The study showed that the haemodynamic effects of propranolol were dissipated 72 hr after the drug was discontinued, but some effects were still present at 48 hr. The haemodynamic effects seemed to outlast detectable serum levels.

a. Respiratory effects

Bronchial muscle tension depends in part on a balance between parasympathetic bronchoconstrictor activity and its inhibition by the sympathetic nervous system. The latter is mediated through beta receptors, and therefore it might be anticipated that blockade of these receptors would result in narrowing of the airways.

McNeil and Ingram (1966) studied the effects of intravenous propranolol and of 10 ml of saline given intravenously as a control on the forced expired volume in one second (FEV1) of 10 asthmatic subjects. The same procedure was followed in 5 normal subjects who also had airway resistance measured with whole body plethysmography (Dubois et al., 1956). In 4 of the 10 asthmatic subjects there was a prompt fall in FEV_1 to half the control value

after propranolol. In the other 6, FEV_1 fell but not significantly. In 5 normal subjects there was no significant change in FEV_1 after propranolol. All 5 normal subjects showed a rise in airways resistance within 30 min of receiving propranolol, and this rise was greater than the expected normal variation. Thoracic gas volume was not measured and therefore resistance changes may have been partly due to changes in lung-volume.

Richardson and Sterling (1969) studied the effects of intravenous propranolol on specific airway-conductance in 10 normal subjects and five subjects with asthma. Airway resistance and thoracic gas volume were measured by means of a constant-volume whole-body plethysmograph (Dubois et al., 1956) and results expressed as changes in specific airway conductance, thus allowing for the effects of changing lung volume on airway resistance. There was a consistent fall in specific airway-conductance after propranolol in the asthmatics, but 3 of the 10 normal subjects showed small falls. Saline alone had no effect in either group. The fall of specific conductance in the healthy subjects was insignificant by t test. Previously reported rises in airway resistance in normal subjects after propranolol may have been partly due to a decrease in lung volume. The authors thought that there is probably a wide variation in individual response to propranolol. Five of 18 subjects reported by MacDonald et al. (1967) showed increases in airway resistance of less than 15% but in two it was 300% or more.

Stone et al. (1971) reported the effects of β-adrenergic inhibition on ventilation, respiratory gas exchange, FEV_1, and arterial blood gases in 10 subjects with chronic bronchitis. After propranolol infusion a significant decrease in heart rate averaging

11 beats min^{-1} occured. Propranolol had no significant effect on ventilation, respiratory frequency or tidal volume. $\dot{V}O_2$ and $\dot{V}CO_2$ were unchanged. In 7 patients FEV_1 fell a little; this decrease averaged 200 ml and was not significant. $PaCO_2$, PAO_2 and $\dot{V}_A$ were essentially the same as during the control period. PaO_2 was significantly higher after propranolol (mean 72, SD 13 mm Hg before, mean 77, SD 15 mm Hg 20 min after). $\Delta AaPO_2$ was thus reduced after propranolol and the authors concluded that this must reflect improved ventilation-perfusion relationships.

It seems from these studies that the effects of β-adrenergic blockade on pulmonary function in subjects with normal lungs may be minimal. Haemodynamic effects may be more important.

b. Cardiac effects

Hamer and Sowton (1965) measured cardiac output, by the Fick method, in 8 patients with ischaemic heart disease but apparently good myocardial function. Blood was obtained directly from the brachial and pulmonary arteries and analysed for O_2-content by the Van Slyke method. Oxygen consumption and $\Delta a\bar{v}C_{O_2}$ were measured at rest and during sitting exercise, before and 15 min after the intravenous injection of 5 mg of propranolol. The cardiac output showed a consistent fall of approximately 22% both at rest and on exercise after propranolol. Results were as follows:

	Before propranolol		After propranolol	
	Rest	300 Kpm/min	Rest	300 Kpm/min
$\dot{Q}t$ ($l.min^{-1}$)	5.0	10.5	3.8	8.3
$\dot{V}O_2$ ($ml.min^{-1}$)	295	965	280	880
$\Delta a\bar{v}C_{O_2}$ ($ml.l^{-1}$)	62	92	77	107
Heart rate (min^{-1})	80	105	71	88
Stroke volume (ml)	66	104	58	97

The fall in $\dot{Q}t$ both at rest and on exercise was significant ($P < 0.02$).

Astrӧm (1968) reported a similar study which included 5 normal people (aged 19-23 yr) and 8 with angina (aged 38-56 yr). $\dot{Q}t$ was measured by the Fick method. Only resting values are shown. Five to 10 mg propranolol was given intravenously and measurements repeated 15 min after the infusion.

	Healthy subjects		Patients with angina	
	Before	After	Before	After
$\dot{Q}t$ ($l.min^{-1}$)	8.8	6.2	6.8	5.0
$\dot{V}O_2$ ($ml.min^{-1}$)	292	260	272	253
$\Delta a\bar{v}C_{O_2}$ ($ml.l^{-1}$)	35.8	42.6	42.0	51.4
Heart rate (min^{-1})	84	70	79	71
Stroke volume (ml)	106	92	85	72

$\dot{Q}t$ fell by 29% in the healthy subjects and by 26% in the patients with angina after propranolol. $\dot{V}O_2$ fell by 11% and 7% respectively.

Thus it seems the acute effect of intravenous propranolol is to increase $\Delta a\bar{v}C_{O_2}$ by approximately 20%. Whether this increase

persists with long-term oral therapy is uncertain. Even more uncertain are the possible changes in $\Delta a\bar{v}C_{O_2}$ that might be expected to follow the termination of chronic, oral β-blocker therapy.

Conclusions from the review of the literature and objectives of the study

This review of the literature shows that many factors influence the pulmonary changes which follow operations using CPBP. Important among these factors are the techniques used to accomplish the bypass and the state of the patients' hearts and lungs before the operation. The reported studies of gas exchange following CPBP leave a gap in knowledge concerning the effects of bypass performed with modern techniques and in patients with preoperatively "nearly normal" lungs. It seemed worthwhile to measure in detail the pulmonary physiological changes in such a group. This study would quantitate the smallest changes in lung function that might be expected to follow CPBP at Green Lane Hospital. The changes measured would provide a baseline with which to compare future studies. For example, if a change in bypass technique was introduced the benefits could be assessed by comparing the results of the present study with those measured in a matched group of patients operated on using the new technique. The baseline results would also allow interesting comparisons with other groups of patients eg. those with severe valve disease and abnormal lungs before operation. It would also be of interest to compare the present changes with those reported previously and with the pulmonary changes reported to follow major operations without CPBP. It was hoped that this study would add to the understanding of the mechanisms producing the deterioration in gas exchange and perhaps reveal a preoperative test that would identify those at special risk from developing respiratory complications.

Materials and Methods

Subjects

Ten patients were studied. The purposes of the study and the procedure were explained to each patient and those asked to take part all assented freely. There were no complications attributable to the investigations. All patients had severe angina pectoris and their symptoms and coronary angiographic abnormalities were such that operation was recommended urgently. The patients all were or had been heavy cigarette smokers. They were selected to have as "normal" lungs as possible, judged by clinical history and examination, chest x-ray and lung volumes. One patient (No. 1) had had early morning cough and sputum for two years but the others denied respiratory symptoms. Little importance can be attached to a denial of effort dyspnoea in a group that is so incapacitated by effort angina. Table 15 shows details of the subjects' preoperative assessment. These were judged according to normal values for VC by Needham et al. (1954), FEV_1/VC by Grimby and Soderholm (1963), FRC and RV by Bates et al. (1971), RV/TLC by Grimby and Soderholm (1963), CV/VC by Buist and Ross (1973) and SRaw by unpublished normal data obtained in this laboratory; the upper 95%-confidence limit for SRaw at all ages is 10.5 sec. cm H_2O. Not surprisingly in a group of smokers there were several with abnormalities of residual volume (RV), residual volume/total lung capacity ratio (RV/TLC) and closing volume/vital capacity ratio (CV/VC).

An attempt was made to study only those patients who seemed to have normal left-ventricular function preoperatively. Left ventricular function was judged by the cardio-thoracic ratio

Table 15.

Patient	Age (yr)	Ht (cm)	Wt (kg)	Smoking	Chest x-ray	Preoperative data: FEV_1/VC %N	FRC(ml) %N	RV(ml) %N	RV/TLC %N	CV(ml)	CV-ERV(ml) S	CV-ERV(ml) L	CV/VC %N	SRaw ($S.cmH_2O$)	ECG	LVEDP (mm Hg)	L.V.Ejection Fraction (%)
1. H.L.	52	169	76	20/day	C.T.R. = 16/32 increased lung markings	81 112	3740 108	2880 142*	43 143*	808	-50	+310	24.7 129*	15.1	sinus rhythm ST depression on exercise	8	66
2. R.W.	40	174	72	20/day	C.T.R. = 15/30.5 lung fields normal	84 109	2560 70	1360 69	24 90.6	515	-650	-200	13.5 91	4.8	sinus rhythm t waves inverted V_4-V_6	10	70
3. L.S.	63	174	61	30/day until 1972 now 5/day	C.T.R. = 15.5/31 lung fields normal	63 92	4230 115	2890 124	42 117	1050	-290	+370	31 135*	6.6	sinus rhythm L.B.B.B.	11	66,5
4. T.D.	49	175	78	non-smoker smoked 50/day until 1972	C.T.R. = 17/33 small areas of subsegmental collapse at bases ? old pneumonia	79 107	3640 97	2410 112	40 140*	590	-640	+138	18.1 100	2.8	sinus rhythm T wave inversion V_4-V_6	30	angio unsatisfactory
5. N.G.	68	166	68	20/day	C.T.R. = 14.5/33 normal lung fields ?? interstitial nodules	68 102	2880 88	2290 106	45 125*	632	+40	+510	32.6 131*	9.3	sinus rhythm T waves flat V_4-V_6	14	58
6. E.T.	50	174	70	25/day	C.T.R. = 13.5/31.5 lung fields normal	72 96	3760 102	2110 99	31 103	720	-930	+140	18 98	8.4	sinus rhythm T wave inverted in aVL and V_4-V_6	16	75
7. J.W.	48	175	75	Now 1-2/day 20/day until 1975	C.T.R. = 13.5/34 lung fields normal	75 102	3320 89	2390 112	33 114	560	-370	+70	12.9 73	14.2*	sinus rhythm normal	12	71
8. J.D.	51	183	66	20/day	C.T.R. = 15/33 lung fields normal	82 112	4870 117	3190 132*	37. 119	1140	-536	-25	23 122	6.6	sinus rhythm T wave flat in aVL otherwise normal	8	56
9. K.W.	60	173	84	non-smoker 30/day until 1972	C.T.R. = 14/31.5 normal lung fields	86 129	2770 76	1920 81	32 103	1020	+166	+686	28.4 129*	4.6	sinus rhythm left anterior hemiblock	8	71
10. S.H.	50	181	75	15/day	C.T.R. = 14.5/32 lung fields normal	79 107	2920 72	1960 72	30 102	1030	-200	+130	27.8 151*	7.6	sinus rhythm	10	58

*, abnormal. %N, percentage of the expected normal value, C.T.R., cardiothoracic ratio. LVEDP, left ventricular end-diastolic pressure.
S, sitting. L, lying.

from a postero-anterior chest x-ray, the electrocardiogram, the left-ventricular end-diastolic pressure and the ejection fraction from a left-ventricular cine-angiogram. One patient had a left ventricular end-diastolic pressure of 33, one 16 and one 14, but all the others were less than 12 mm Hg (zero reference point; 4th intercostal space in the mid-axillary line).

All the patients were receiving β-adrenergic blocking drugs at the time of their preoperative assessment. Patients 1, 4 and 5 were taking digoxin 0.25 mg daily and 5 was also taking frusemide 40 mg daily. β-blockers were stopped 12-15 hr before operation in all cases, and were not restarted. All patients had 1.5 mega units of benzylpenicillin and 0.5 g streptomycin 12-hourly, intramuscularly for 4 days after operation. The benzylpenicillin was then continued for a further 4 days alone. All patients also had 5,000 units of heparin, subcutaneously, for 7 days, starting 48 hr after operation. Digoxin 0.25 mg daily was also started at this time.

Procedure

Ten days or less before operation, the patients underwent cardiac catheterization. Coronary angiograms and left ventriculograms were performed. The subjects were premedicated with pentobarbitone (100 mg), butobarbitone (60 mg) or diazepam (15 mg). Following the angiograms the aortic catheter was replaced by a shorter arterial sampling-catheter and a second catheter advanced from an arm vein until its tip lay in the pulmonary artery. The patients were then transferred to the nearby lung function laboratory where measurements of pulmonary blood-gas exchange were made. The patients were studied semirecumbent, approximately in the position they would later occupy

in the postoperative intensive care ward. The subjects first breathed air through a respiratory valve for at least 5 min or until the breathing pattern was regular; a Douglas bag was then washed out twice with expired gas, and a timed, 6 min expired sample was collected. An 8 ml sample of arterial blood and an 8 ml sample of mixed-venous blood were drawn at a uniform rate into heparinized glass syringes during the 3rd and 4th min of this collection. The syringes were not previously iced and contained a stainless-steel washer so that blood and heparin could be thoroughly mixed. During the collection of expired air, a record of N_2 concentration at the mouth was made, from which respiratory frequency could be determined. Inspired gas was then switched from air to oxygen (mean O_2 concentration 0.9973) near the end of a tidal expiration, and the process of N_2-washout recorded breath by breath. When end-tidal N_2-concentration was below 0.010 another Douglas bag was washed out twice and a second 6-min sample of expired gas was collected, with arterial and mixed venous samples taken as before.

Two or three days after the above investigation the patients returned to the pulmonary laboratory for measurement of lung volumes and airway resistance. Slow and forced spirograms were made. Specific airway-resistance functional residual capacity and closing volume were measured in the sitting position (FRC was also calculated from the N_2-washout, semirecumbent, during the gas-exchange study). A further slow spirogram was made in the supine position and the expiratory reserve volume measured.

At operation, total CPBP was begun using a Bentley/Temptrol Q100 bubble-oxygenator and a circuit similar to that described by Barratt-Boyes (1965). A bloodless prime, consisting of 700 ml 5%

dextrose, 300 ml 15% mannitol, 1500 ml lactated Ringers and 15 m equ. potassium chloride, was used. The patients were cooled to a naso-pharyngeal temperature of 30 or 32°C. Flows were maintained at 2 $l.min^{-1}.m^{-2}$ during the operation and at 2.4 $l.min^{-1}.m^{-2}$ during rewarming. The saphenous vein was used as a graft to bypass coronary obstruction from aorta to distal coronary artery. For the distal anastomosis of each graft the aorta was cross-clamped, and the duration of these periods is shown in Table 16. The proximal anastomosis to aorta was made with aortic side-clamping and therefore flow was available to the coronary arteries. The patients were rewarmed and a nylon catheter passed obliquely through the right-ventricular wall until its tip lay in the pulmonary artery. The other end of this catheter was led out through a stab incision below the xiphoid cartilage. The chest was then closed. The pulmonary-artery catheter was left in place until 48 hr after the operation and was used to sample mixed-venous blood during the postoperative studies.

Premedication for the operation was generally papaverretum 20 mg and hyoscine 0.4 mg given intramuscularly 1 hr before hand. Three patients had pethidine and promethazine (0.75 $mg.kg^{-1}$ of each) and hyoscine as premedication. Anaesthesia was induced with thio-pentone followed by D-tubocurarine and maintained with nitrous oxide and oxygen. Additional relaxant was given as necessary and halothane in low concentration (usually 0.5%) was added to the oxygenator gases during perfusion. Atropine and neostigmine were given routinely at the end of the operation. None of the patients in this study needed cross-matched donor blood during CPBP. At the end of CPBP all the blood remaining in the circuit was collected into bags and transfused

to the patients as required postoperatively. Several of the patients needed fresh cross-matched donor-blood in addition during the post-operative period (see table 16). Only donor blood which was less than 5 days old was used.

None of these patients required artificial ventilation after recovery from the anaesthetic. Pain and discomfort were minimised by repeated intravenous doses of diazepam and/or papaveretum, but the patients all remained awake and rational at the time of the studies. As nearly as possible at 8, 22, 28 and 48 hr after operation the blood gas-exchange and N_2-washout measurements described for the preoperative study were repeated. At the end of the study the pulmonary-artery catheter was pulled out; there were no complications from this source.

A final respiratory study was carried out at approximately 10 days after operation. A further pulmonary-artery catheter was inserted at this time and some patients had coronary angiographic studies before the gas exchange study was made. Only 5 patients completed the full sequence of pulmonary studies; the other 5 became disinclined, through fatigue and postoperative depression, to allow tests to be made at some of the times. All patients completed the first 3 studies, namely up to and including the 22 hr postoperative one.

Laboratory measurements

Figure 10 is a photograph of the system used for the blood-gas exchange and N_2-washout measurements. Wall air or oxygen was supplied to the flaccid demand bag at approximately the subject's ventilation rate. The mouth piece was attached to a Hans Rudolph

Figure 10. Photograph of the apparatus used for the blood-gas exchange and N_2-washout measurements. The system is described in the text.

valve which had a nitrogen-sampling needle just distal to the lips. Nitrogen concentration, measured with a Hewlett-Packard 47302A Nitrogen analyzer, was recorded on the Y axis of a Riken Denshi XY-YT recorder. The output of the N_2 analyzer was linear to within 1% over the range 0 to 80%. Time was recorded on the X-axis of the recorder. Respiratory frequency was counted from the recorder trace by the inspiratory and expiratory fluctuations of N_2 concentration. A hand-operated switch just proximal to the inspiratory port of the Hans Rudolph valve allowed the patients to breathe either from the demand bag or from room air. Before starting the N_2 washout it was therefore possible to wash the circuit and demand bag thoroughly with O_2 and then, on changing the switch, the subject inspired pure oxygen. The total valve dead space was 36 ml. The expiratory port of the Hans Rudolph valve was connected to a Douglas bag placed out of the patient's sight.

Gas volumes in the Douglas bags were measured with a dry gas-meter (Parkinson and Cowan CD4) calibrated against a Tissot spirometer. Concentrations of O_2 and CO_2 were measured with a Servomex OA 150 paramagnetic analyzer and a Hartman and Braun URAS-M infra-red analyzer respectively, the outputs of each being read on a digital voltmeter (Ellis and Nunn, 1968; Harris, 1973). 95%-confidence limits for a single measurements of F_{O_2} were ± 0.036 and of FCO_2 ± 0.023.

Partial pressures of O_2 and CO_2 and pH in blood were measured with Radiometer electrodes E5036, E5046 and G297/G2 and a PHM72 electrometer. The PO_2 reading was taken according to Severinghaus and Bradley (1971) and was corrected for the gas/blood factor, determined after each experiment by tonometry (Farhi, 1965),

for dilution with heparin (Lübbers, 1966), for any small differences between the electrode's and the patient's oral temperature (never > 0.2°C), and for the time between sampling and measurement, obtained by stopwatch and never more than 5 min (Kelman and Nunn, 1966). Haemoglobin concentration (Hb) was measured by the optical absorption of cyanmethaemoglobin at a wavelength of 540 nm. 95%-confidence limits for the mean of a duplicate determination were ± 1.3 g. l^{-1}. Arterial and mixed-venous O_2 saturation were measured with a Radiometer OSM 1 spectrophotometer; 95%-confidence limits for the mean of a triple estimation were ± 0.87% for arterial and ± 1.40% for venous blood.

Calculations

Oxygen consumption, carbon dioxide output and gas exchange ratio were calculated by conventional methods (Douglas and Priestley, 1948). $\dot{V}O_2$ during O_2-breathing was assumed to be the same as the corresponding air-breathing $\dot{V}O_2$. Physiological deadspace volume was calculated from tidal volume and $PaCO_2$ and P_ECO_2 by Enghoff's modification of the Bohr equation (as in Part I). The valve dead space volume (36 ml) was subtracted from the calculated value. Alveolar PO_2 breathing air and O_2 was calculated as in Part I. In the first 5 patients in the CPBP study, air breathing F_{IO2} was assumed to be 0.2094. At this stage some doubts arose as to the constancy of the wall air-supply and on the subsequent 22 air-breathing studies wall air F_{IO2} was measured and averaged 0.2085 (SD 0.06). In each experiment the appropriate measured F_{IO2} was used in these 22 studies. The error in calculation of PAO_2 using the assumed F_{IO2} of 0.2094 instead of the average measured F_{IO2} of 0.2085 is 0.6 mm Hg.

Venous admixture was calculated using the modified shunt equation:

$$\dot{Q}va/\dot{Q}t = (C\acute{c}O_2 - CaO_2)/(C\acute{c}O_2 - CaO_2) + (CaO_2 - C\bar{v}O_2)$$

$C\acute{c}O_2$ and CaO_2 were calculated from Kelman's computer subroutine (1966) as before. $\Delta a\bar{v}C_{O_2}$ was measured from SaO_2, $S\bar{v}O_2$, Hb, PaO_2 and $P\bar{v}O_2$ according to the equation $C_{O_2} = (SO_2 \times Hb \times K) + \alpha PO_2$, where K is the O_2 capacity of 1 g of haemoglobin, determined separately on residual blood from the preoperative study, on pooled blood from the 8, 22, 28 and 48 hr postoperative studies, and on blood from the 10 day postoperative study by the method of van Slyke and Neill (1924). α is the solubility of oxygen at the patient's oral temperature. $\dot{Q}t$ was derived from $\dot{V}O_2$ and $\Delta a\bar{v}C_{O_2}$ via the Fick equation.

T-tests, linear regressions and correlation coefficients were calculated by standard methods (Davies, 1961). The two tailed probability (2P), calculated by paired t-test, that changes in the variables were due to chance is shown in the tables of results. The significance levels quoted should be interpreted with caution as: 1. multiple t-tests were used and thus the likelihood of spurious significance for any individual comparison is greater than the reported P values; 2. in any patient change in one variable is closely associated with change in others. They all describe the health of the patient. Also several of the variables are calculated or derived from others eg. $\dot{Q}t$ from $\Delta a\bar{v}C_{O_2}$ and $\dot{V}_{O_2}$. Thus the variables are not independent.

P values shown may, therefore, overestimate the significance

of the changes. Having accepted these reservations the P values are still of interest in the description of the data. They help to define trends. They have been used to aid in the description of clinical data rather than to confirm or refute hypotheses. The main conclusions from the study do not depend on t-tests, they are based on the patterns of change with time shown for the groups as a whole. These changes are clearly demonstrated in figures 11 and 13 where mean values for the group are shown with 95%-confidence limits of the mean.

Analysis of N_2-washout curves

The nitrogen-washout curves were analyzed in 2 ways, both based on the relationship between the logarithm of end-tidal N_2 concentration and breath number. The Relative Ventilation Ratio (RVR) is calculated, assuming that the lung has only two differentially ventilated compartments - the 'fast' and 'slow' spaces. This gross oversimplification provides a means of expressing the distribution of inspired gas numerically. A plot of log N_2-concentration against breath number for a uniformly ventilated lung with no dead space is a straight line described by the equation,

$$\log Fn = \log Fo + n \log V/(V + \Delta V)$$

where Fn is the N_2-concentration at breath n, Fo the N_2-concentration before the washout starts, V, the lung volume at end-expiration and ΔV the tidal volume. The washout curve of a lung with two such compartments will be a composite derived from both 'spaces'. The plot of log Fn against n will be curved in its first part but its last part will be a straight line, because only the slow space will be contributing nitrogen at this time. If the last part of the

curve is extrapolated to the ordinate, a line characterising the slow space is produced. By difference between the original curve and the extrapolation another straight line is derived which shows the characteristics of the fast space. The two lines then represent washouts from the two spaces as if they washed out separately and in sequence i.e. the fast space first with no N_2 contribution from the slow space and then the slow space washes out as if the fast space were full of O_2. The F_{N_2} at the intercept of each line with the ordinate is dependent on the relative ventilations of the spaces. From the intercepts and slopes of these lines the volume and tidal volume of the fast and slow spaces can be calculated (Vf, ΔVf, Vs and ΔVs). The specific ventilation of each space is thus ΔVf/Vf or ΔVs/Vs and the ratio of these is defined as the Relative Ventilation Ratio $(\Delta Vf/vf)/(\Delta Vs/VS)$. The more specific ventilations of fast and slow spaces differ the more uneven is ventilation. If the lungs were uniformly ventilated the ratio would be 1.0.

A value of FRC can also be derived from this analysis of the N_2-washout curve as FRC = Vf + Vs. This model assumes no dead space so in practice an alveolar tidal volume equal to V_T minus predicted anatomical dead space is used when calculating RVR. The FRC calculated must then have this assumed V_D added to it.

The second way in which the N_2-washout curves were analyzed derives the Index of Alveolar Ventilation (IAV). The calculation and use of the IAV are described by Lichteneckert and Lundgren in 1963. The IAV is defined as the ratio of measured clearance coefficient to ideal clearance coefficient. Measured clearance coefficient is the cumulated volume of O_2 required to lower mean alveolar nitrogen concentration in the lungs being tested from

0.800 to 0.020. The ideal clearance coefficient is calculated as the O_2 required to produce the same fall in F_{N_2} in a lung with identical volumes but in which ventilation is distributed uniformly.

FRC measured by N_2-washout

To assess the measurement of FRC by N_2-washout a comparison was made with FRC measured by whole body plethysmography. In a group of 78 patients referred to the pulmonary function laboratory at Green Lane Hospital, all of whom had technically good N_2 washouts, with RVR < 6 and IAV > 50% the regression equation of plethysmography FRC on FRC measured by N_2-washout (both sitting) was:-

FRC (plethysmograph) = 0.5535 x FRC (N_2-washout) + 1115 ml, $r = 0.7997$, $2P << 0.001$, SD about regression 482 ml.

In this group, therefore, plethysmographic and washout FRC are the same at an FRC of 2.5 l. The washout underestimates low FRCs and overestimates big ones. The mean plethysmographic FRC was 394 ml lower than the mean FRC derived from N_2-washout, and this difference was highly significant by paired t-test ($2P < 0.001$). Nevertheless the high correlation indicates that the washout technique yields a value for FRC closely related to that given by a more conventional method.

Clinical Details

Before discussing the patterns of change in the group as a whole it is necessary to point out that the patients were dissimilar in many respects, despite having been selected from those with clinically normal lungs. Because of the variation between patients, conclusions must be drawn from mean values with some caution. On the other hand the group are representative of the 'fittest' patients having cardiac operations with CPBP at Green Lane Hospital and their preoperative differences and variations in clinical courses are likely to be typical of such patients. The main clinical features which should be considered in assessing differences between patients in postoperative gas exchange are detailed below and are outlined in tables 15, 16A and 16B. The possible correlation between some pre-operative and operative data and the degree of postoperative deterioration will be explored later.

Case-histories

1. H.L. gave a history of childhood asthma which had cleared when he was a teenager. He had had early morning cough and sputum for 2 yr which he attributed to sinusitis. He denied shortness of breath. Before operation he was taking digoxin 0.25 mg daily, propranolol 40 mg t.i.d. and glyceryl trinitrate as required. He had an uncomplicated operation and early postoperative period but on the 6th day after operation developed left-sided pleuritic pain and fever. Chest X-rays had been normal until the 3rd day after operation at which time minor collapse at the left base was present and this appearance persisted for 10 days. Despite the absence of signs in the legs, haemoptysis, chest X-ray or ECG changes supporting

Table 16a. Operative and postoperative data.

Patient	Operation and date	Operation time (min)	Bypass time (min)	Aortic clamp time (min)	X-match blood	Haemoglobin gm 100 ml^{-1} preop.	Days postop. 1	2	10	Enzymes	Days postop. 1	2	Clinical impression
1. H.L.	4, C.V.Gs 8.3.76	260	139	15,20, 24,15= 74	none	14.2	13.2	11.4	11.8	ASP.A.T. H.B.D.	94 237	16 39	Left sided pleuritic pain from 6th to 10th day after operation. Otherwise uncomplicated.
2. R.W.	4, C.V.Gs 10.5.76	315	184	21,25, 26,20= 92	3 litres	14.5	10.2	8.2	11.1	ASP.A.T. H.B.D.	237 397	136 388	Hypotension and chest pain 2 days after operation. ECG and enzymes confirmed perioperative myocardial infarction. Good recovery following this.
3. L.S.	3, C.V.Gs 26.4.76	300	155	22,29, 25=76	1.5 litres	14.0	10.6	10.3	12.5	ASP.A.T. H.B.D.	164 385	104 300	Mild left hemiparesis 6 hr after operation. Complete recovery by 10th day. Atrial fibrillation postoperatively but reverted spontaneously No chest complications
4. T.D.	1, C.V.G. 17.5.76	160	51	26	none	13.0	13.0	11.5	11.1	ASP.A.T. H.B.D.	32 159	23 169	Cough and purulent sputum from 2nd to 9th day after operation. Otherwise uncomplicated.
5. N.G.	3, C.V.Gs 16.6.76	270	124	28,19, 21=68	2.0 litres	13.8	12.4	12.1	9.9	ASP.A.T. H.B.D.	38 176	60 213	White sputum from days 3-8. Otherwise uncomplicated.

C.V.G., coronary vein graft; ASP.A.T., aspartate aminotransferase (normal 10-50);

H.B.D., hydroxybutyric dehydrogenase (normal 150-300).

Table 16b.

Patient	Operation	Operation time (min)	Bypass time (min)	Aortic clamp time (min)	X-match blood	Haemoglobin gm 100 ml^{-1} Preop.	Days postop. 1	2	10	Enzymes Days postop. 1	2	Clinical impression
6. E.T.	2, C.V.Gs 24.8.76	240	113	33,27=60	1.5 litres	14.5	12.0	10.6	9.6	ASP.A.T. 78 H.B.D. 282	- -	Cough & white sputum from 2nd to 5th day with reduced air entry at R.L.Z. Otherwise uncomplicated
7. J.W.	3, C.V.Gs 7.10.76	260	139	19,20, 19,17=75	1.0 litres	13.2	12.7	10.3	10.3	ASP.A.T. 34 H.B.D. 190	- -	No complications
8. J.D.	3, C.V.Gs 29.6.76	320	144	25,24, 23=72	0.5 litres	13.1	13.8	13.0	12.4	ASP.A.T. 37 H.B.D. 158	35 177	Left sided pleuritic pain, cough & green sputum at day 5. Otherwise uncomplicated
9. K.W.	4, C.V.Gs 23.3.76	260	137	Total 110	1.5 litres	12.8	11.5	10.5	10.0	ASP.A.T. 35 H.B.D. 58	172 138	Cough & white sputum from days 2-6. Recurrent angina - 2 of 4 grafts shown to be occluded at a study 10 days after operation
10. S.H.	3, C.V.Gs 16.8.76	305	149	23,26, 18=67	none	13.5	13.4	12.4	10.6	ASP.A.T. 50 H.B.D. 242	34 192	No complications.

C.V.G., coronary vein graft; ASP.A.T., aspartate aminotransferase (normal 10-50);
H.B.D., hydroxybutyric dehydrogenase (normal 150-300).

a diagnosis of pulmonary embolus, the latter could not be excluded and warfarin was started. He made an uneventful recovery following anticoagulation but still had slight pleuritic pain at the time of his 10-day postoperative gas exchange study.

Postoperatively he remained in sinus rhythm. ECGs were unremarkable, showing only minor T-wave changes in leads V_3 - V_6. The T waves had become normal when he was seen 3 weeks after operation.

2. R.W. was well before operation apart from severe angina. He was taking propranolol 160 mg daily and glyceryl trinitrate as required. He required unusually large amounts of fluid additions during CPBP and was hypotensive shortly after coming off CPBP, but improved with rapid infusion of pump and cross-matched blood. For the first day after operation he continued to bleed excessively, draining 2 litres in the first 24 hr and requiring further cross-matched blood. He remained in sinus rhythm, normotensive and comfortable at the time of his 8, 22 and 28 hr studies but by 40 hr postoperatively he had developed chest pain and become hypotensive and short of breath. Serum enzyme levels and ECGs confirmed that he had had a perioperative myocardial infarction. His peripheral circulatory failure was treated with cautious blood-transfusion and digitalisation. He improved steadily after this and had no symptoms when seen as an outpatient 6 weeks after his operation. No gas exchange studies were done after 28 hr postoperatively. Chest X-rays showed mild interstitial oedema 48 hr after operation and some enlargement of the heart; the X-rays appeared normal before then. The lung fields were clear one week after operation and the cardio-thoracic ratio was 13/30, two weeks later.

ECGs showed deep Q waves and ST elevation in leads III and AVL 24 hr after the operation.

3. L.S. was well before his operation apart from angina. He was taking timolol maleate 15 mg daily and sorbide nitrate 40 mg daily. He was noted to have a soft right carotid-artery bruit. He had an uneventful operation. Because of sinus bradycardia he had atrial pacing until 10 hr after operation. He remained in sinus rhythm from 10 - 40 hr after operation at which time he developed atrial fibrillation, became confused and showed signs of a slight left hemiparesis. His 48-hr study was difficult and since he would not tolerate a mouthpiece, only arterial and mixed-venous blood samples were taken while he breathed room air. He was digitalised and given a transfusion of 2 units of packed cells, and made good progress following this. Seven days after the operation he was started on quinidine and reverted to sinus rhythm. At the time of his 10-day postoperative study he had recovered from his hemiparesis, was in sinus rhythm and taking digoxin 0.25 mg daily, quinidine bisulphate slow-release tablets 1000 mg daily and potassium chloride 1800 mg daily.

The postoperative chest X-rays were normal apart from a little left-basal pleural reaction. ECGs showed left bundle-branch block and the rhythm changes already described.

4. T.D. had no symptoms apart from angina before his operation. He had mild maturity-onset diabetes mellitus and reactive depression. He was taking timolol maleate 30 mg daily, glibenclamide 5 mg each morning and 2.5 mg at mid-day, chlordiazepoxide 15 mg daily, clofibrate 2000 mg daily, trimipramine 50 mg

nocte and glyceryl trinitrate as required at the time of his preoperative study. Only one saphenous-vein graft was made to the left anterior descending coronary artery and the operation was uncomplicated. Because of sinus bradycardia soon after operation he had atrial pacing for the first 2 hr but after this remained in sinus rhythm. By the second postoperative day and at the time of the 48 hr study he had developed a cough and purulent sputum. His chest was dull to percussion over the right lower lung zone and chest X-rays by 36 hr showed fairly severe bilateral basal atelectases. By the 10th day after operation the basal atelectases were resolving, though not completely clear, and he was free from symptoms. Unfortunately he refused to have a 10-day study.

5. N.G. was the oldest of the group but admitted to no chest symptoms other than anginal pain. At the time of his preoperative study, each day, he was taking digoxin 0.25 mg, frusemide 40 mg, potassium chloride 2400 mg, oxprenolol hydrochloride 160 mg, verapamil 160 mg and nitrazepam 5 mg at night. As premedication for his cardiac catheter study he had diazepam 10 mg and this made him very drowsy. During the preoperative gas exchange measurements his breathing pattern was quite irregular and this periodic breathing was noticed again during his postoperative tests. His operation was uncomplicated and postoperatively the only problems were some confusion for 2 days (atributed to previous high alcohol intake) and cough with white sputum from day 2 to 8. His chest X-rays after operation were described by the radiologist as being "as good as you could hope to see" and the lung fields showed virtually no change from the preoperative films. ECGs showed minor anterior T wave changes for 10 days after the operation.

6. E.T. had angina but no respiratory symptoms. At the time of his preoperative gas exchange study he was taking, each day, oxprenolol hydrochloride 240 mg, sorbide nitrate 30 mg, cyclopenthiazide 0.5 mg (for mild hypertension) and glyceryl trinitrate as required. His operation and postoperative course were uncomplicated. He had a little cough and colourless sputum from day 2 to day 6 and chest X-rays showed plate atelectasis at the right and left lower zones from the 2nd day after operation. E.T. completed all the studies and by the 10-day study his chest X-ray was clearing and he was taking digoxin 0.25 mg and ferrous sulphate 900 mg daily. Again the only ECG changes were of anterior T wave flattening for 3 or 4 days after the operation.

7. J.W. had no history or symptoms of note other than his anginal pain. At the time of his preoperative study he was taking propranolol 240 mg and sorbide nitrate 40 mg daily. He developed a severe urticarial rash 4 days before operation and as this did not resolve with chlorpheniramine maleate he was given prednisolene in rapidly decreasing dosage. He had 10 mg of prednisolone on the day before his operation and 50 mg hydrocortisone i.v. q.i.d. the day of the operation and 25 mg i.v. q.i.d. on the 1st day after operation. The hydrocortisone was then stopped. His operation and postoperative course were entirely uncomplicated. One day after operation his chest X-ray showed slight subsegmental atelectasis in both mid-zones and these had cleared at the time of the 10-day postoperative study. The ECGs appeared to be unchanged by the operation.

8. J.D. had no symptoms referable to the respiratory

tract. He was taking propranolol 240 mg, and glyceryl trinitrate as required each day. His operation was uncomplicated and he remained well until 40 hr after the operation, at which time he began to complain of substernal pleuritic chest pain and developed a cough with green sputum. Sputum culture produced no obvious pathogenic bacteria but he was given cephalexin 500 mg q.i.d. orally from the 2nd to the 7th postoperative days. Chest X-ray 24 hr after the operation showed left lower zone collapse and consolidation and there were small bilateral pleural effusions. Radiologically, pleural changes were still present 6 weeks after operation and the patient still had occasional pleuritic pain. The radiologist thought that the persistence of these changes might indicate that the patient had had postoperative pulmonary embolism or some form of postpericardiotomy syndrome. There was no other evidence to support the latter diagnosis. ECGs showed sinus rhythm and T wave inversion in leads V_3 - V_5 which were still present at the time of his discharge from hospital. At the 6-week out-patient visit the ECG was normal, once again.

9. K.W. had a long history of angina. He denied having any respiratory symptoms but had suffered from "colitis" for several years. He was taking propranolol 120 mg, dicyclomine hydrochloride 30 mg and glyceryl trinitrate as required, each day. His operation was uncomplicated but his distal coronary vessels were found to be extensively diseased and rather unsatisfactory for grafting. He made a good early postoperative recovery and only had minimal cough with colourless sputum from the 2nd day. On being mobilised 6 days after operation he had recurrence of anginal pain and a further coronary angiogram at 10 days showed that 2 of his grafts had

become occluded. Chest X-ray showed plate atelectasis at both bases 2 days after operation and markedly raised diaphragms. Only minimal plate atelectasis at the right base remained at the time of the late postoperative study. ECGs showed persistent sinus rhythm with T wave inversion in V_4 - V_6 for 4 days after operation.

10. S.H. had no symptoms other than angina and was taking propranolol 160 mg and sorbide nitrate 40 mg daily, up to the time of his operation. There were no problems at operation, but he had sinus bradycardia soon afterwards and had atrial pacing for the first 12 hr. He completed his 22 hr study but the radial artery catheter blocked at this stage and he was reluctant to have any more tests. This was a pity as his postoperative course was quite uncomplicated. His lung fields appeared clear on the chest X-rays taken at the times of the 8 and 22 hr studies. ECGs showed T wave inversion in the anterior chest leads until the time of his discharge. These had returned to normal when he was seen at the out-patients' clinic 6 weeks after operation.

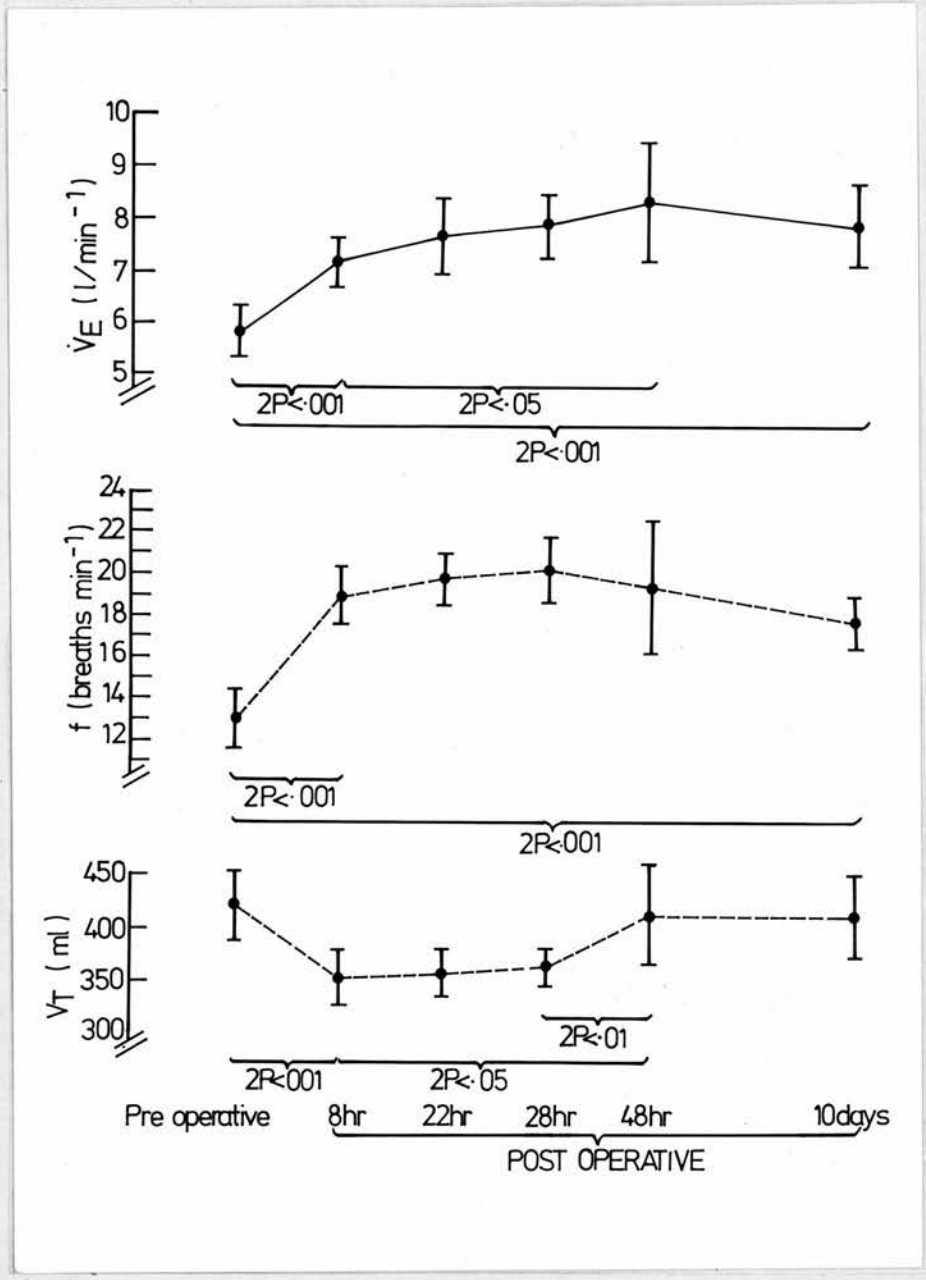


Figure 11. Pre- and postoperative values for $\dot{V}_E$, f and V_T. Air- and O_2-breathing results have been combined and mean values for the group at each time are shown. The bars enclose 95%-confidence intervals of the means.

Results

Individual and mean values of V_T, f, $\dot{V}_E$, $PaCO_2$, pH, PaO_2, PAO_2, $\Delta AaPO_2$, $\dot{Q}Va/\dot{Q}_t$, V_D, $\dot{V}_{O2}$, $\dot{Q}t$, $\Delta a\bar{v}C_{O_2}$, R, FRC, RVR and IAV are shown in tables 17-34.

Pattern of ventilation

Tables 17, 18 and 19 show pre- and postoperative values for V_T, f and $\dot{V}_E$. In figure 11 the same variables are plotted with mean values for the group derived by combining air- and O_2-breathing results at each time.

Air-breathing tidal volume and O_2-breathing tidal volume were not significantly different at any time. Results were, therefore, combined in comparing different times. V_T was significantly smaller than the preoperative value at 8, 22 and 28 hr postoperatively. At some time between 28 and 48 hr V_T returned to the preoperative level and remained there 10 days after the operation.

Air-breathing respiratory frequency differed significantly from the corresponding O_2-breathing frequency only in the preoperative study. The mean value of all air-breathing frequencies was 18.08 and of all O_2-breathing frequencies was 18.03 ($2P > 0.80$). It therefore seemed reasonable to combine both in comparing different times. Postoperative respiratory frequency was higher than the preoperative value at all times. It was still increased at 10 days. There was no significant difference between frequencies at any of the postoperative times.

O_2-breathing $\dot{V}_E$ was significantly higher than the air-breathing value only preoperatively. This was again ignored and combined values were used to compare different times. The mean of all air-breathing $\dot{V}_{Es}$ was 7.31 and O_2-breathing it was 7.41

($2P > 0.40$). $\dot{V}_E$ was significantly higher than the preoperative level at all times after operation. $\dot{V}_E$ rose progressively to 48 hr postoperatively and had fallen a little from this level by 10 days.

To summarise: pulmonary ventilation was increased after CPBP and this increase persisted at 10 days after operation. Initially after operation tidal volume was reduced and the increased $\dot{V}_E$ was achieved entirely by a large increase in f. When V_T returned to the preoperative level between 28 and 48 hr respiratory frequency remained high and $\dot{V}_E$ increased further.

Table 17. Tidal volume (ml).

Subject	Preop		8 hr		22 hr		28 hr		48 hr		10 days	
	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2
1. H.L.	444	471	300	316	389	396	335	358	348	328	534	465
2. R.W.	412	406	315	331	303	314	326	350				
3. L.S.	510	391	397	373	391	350	372	368			361	353
4. T.D.	388	424	324	338	297	341	274	315	260	343		
5. N.G.	273	281	211	308	261	340	417	417	493	520	312	402
6. E.T.	518	525	427	299	377	308	338	394	499	522	480	426
7. J.W.	502	459	435	412	433	438	380	372	413	376	365	474
8. J.D.	366	427	403	335	333	344	348	325	378		350	375
9. K.W.	287	351	322	347	373	363	377	377	412	424	362	464
10. S.H.	474	480	387	407	379	349						
MEAN	417	422	352	347	354	354	352	364	400	419	395	423
	2P > 0.80		2P > 0.7		2P > 0.95		2P > 0.10		2P > 0.4		2P > 0.3	

For comparisons air and O_2 values combined.

MEAN	419	349	354	358	409	409
SD	77.8	55.2	45.0	36.0	81.3	65.1
N	20	20	20	18	13	14

Times	2P	Times	2P
Pre - 8 hr	<0.001	8 - 22 hr	>0.60
" - 22 hr	<0.001	8 - 28 hr	>0.4
" - 28 hr	<0.05	8 - 48 hr	<0.05
" - 48 hr	>0.95	22 - 28 hr	>0.70
" - 10 days	>0.80	28 - 48 hr	<0.01
		48hr-10days	>0.80

Table 18. Respiratory frequency (f) (breaths min^{-1}).

Subject	Preop		8 hr		22 hr		28 hr		48 hr		10 days	
	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2
1. H.L.	13.66	13.66	23.00	23.00	24.33	23.33	23.00	24.00	24.00	25.30	17.50	16.83
2. R.W.	9.83	12.67	19.50	18.33	21.17	18.67	22.50	20.00				
3. L.S.	10.00	13.00	15.50	15.50	20.40	21.17	21.67	21.67			17.33	17.33
4. T.D.	14.50	14.00	16.67	17.00	21.67	22.00	23.00	24.67	21.17	21.67		
5. N.G.	11.17	14.00	23.33	22.83	14.50	16.33	13.33	13.33	10.50	10.67	19.33	16.00
6. E.T.	11.17	11.67	18.50	18.00	19.33	17.17	18.83	19.33	15.63	14.67	17.50	18.00
7. J.W.	10.33	12.17	15.83	15.83	17.50	15.00	17.67	16.67	17.83	19.00	19.00	17.78
8. J.D.	11.00	12.00	16.67	17.83	18.50	18.67	17.83	19.50	19.83		14.67	14.67
9. K.W.	21.17	20.50	24.00	23.00	22.00	22.00	23.30	23.30	27.00	25.00	22.17	19.33
10. S.H.	10.00	12.33	19.33	15.00	20.17	20.33						
MEAN	12.28	13.60	19.23	18.63	19.96	19.47	20.13	20.27	19.42	19.39	18.21	17.13
	2P < 0.02		2P > 0.20		2P > 0.30		2P > 0.70		2P > 0.95		2P > 0.10	

For comparisons air and O_2 values combined.

MEAN	12.94	18.93	19.71	20.20	19.41	17.67
SD	3.06	3.12	2.67	3.44	5.39	1.95
N	20	20	20	18	13	14

Times	2P	Times	2P
Pre - 8 hr	<0.001	8 - 22 hr	>0.30
" - 22 hr	<0.001	8 - 28 hr	>0.30
" - 28 hr	<0.001	22 - 28 hr	>0.10
" - 48 hr	<0.001	28hr-10days	>0.05
" - 10 days	<0.001	48hr-10days	>0.50

Table 19. Ventilation rate ($l.min^{-1}$).

Subject	Preop		8 hr		22 hr		28 hr		48 hr		10 days	
	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2
1. H.L.	6.56	6.93	7.73	8.09	10.34	10.07	8.53	9.45	9.22	9.22	9.96	8.43
2. R.W.	4.40	5.60	6.85	6.72	7.18	6.54	8.16	7.72				
3. L.S.	5.46	5.55	6.71	6.34	8.71	8.16	8.84	8.76			6.89	6.75
4. T.D.	6.15	6.44	6.00	6.36	7.22	8.28	7.14	8.67	6.28	8.21		
5. N.G.	3.45	4.44	5.76	7.86	4.31	6.14	6.03	6.03	5.56	5.93	6.73	7.01
6. E.T.	6.18	6.54	8.57	6.02	7.99	5.91	7.04	8.31	8.36	8.18	9.03	8.31
7. J.W.	5.56	6.02	7.46	7.10	8.21	7.11	7.35	6.80	8.00	7.83	7.62	9.07
8. J.D.	4.43	5.55	7.32	6.62	6.82	7.10	6.85	7.03	8.22		5.67	6.03
9. K.W.	6.84	7.93	8.60	8.81	9.00	8.78	9.63	9.63	12.10	11.49	8.83	9.66
10. S.H.	5.10	6.36	8.18	6.65	8.37	7.83						
MEAN	5.41	6.14	7.32	7.06	7.82	7.59	7.73	8.04	8.25	8.48	7.82	7.89
	2P < 0.001		2P > 0.50		2P > 0.50		2P > 0.20		2P > 0.50		2P > 0.80	

For comparison air and O_2 values combined.

MEAN	5.77	7.19	7.70	7.89	8.35	7.86
SD	1.05	0.93	1.42	1.16	1.91	1.37
N	20	20	20	18	13	14

Times	2P	Times	2P
Pre - 8 hr	<0.001	8 - 22 hr	>0.05
" - 22 hr	<0.001	8 - 48 hr	<0.05
" - 28 hr	<0.001	22 - 28 hr	>0.30
" - 48 hr	<0.001	28 - 48 hr	>0.05
" - 10 days	<0.001	48hr-10days	>0.40

Arterial PCO_2 and pH

Apart from the preoperative values $PaCO_2$ tended to be higher when O_2 was breathed than when air was breathed. There was not a corresponding reduction in total ventilation (see table 19). pH changes were generally what would be expected from $PaCO_2$ changes. Because of the air/O_2 differences both pH and $PaCO_2$ results were analysed separately for air-breathing and O_2-breathing periods.

Mean air-breathing $PaCO_2$ became significantly lower than preoperatively at 22 hr and remained low at 10 days. In fact the fall in air-breathing $PaCO_2$ was progressive throughout the post-operative period. The postoperative fall in $PaCO_2$ was less significant when O_2 was breathed but still apparent. Some individuals had abnormally high $PaCO_2$s especially when O_2 was breathed in the 8 and 22 hr postoperative studies, and mean $PaCO_2$ breathing O_2 was higher at these times than preoperatively. From 22 hr after operation the subjects tended to be more alkalotic than preoperatively.

Table 20. Arterial carbon dioxide tension (mm Hg).

Subject	Preop		8 hr		22 hr		28 hr		48 hr		10 days	
	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2
1. H.L.	39.2	37.1	37.6	37.9	31.0	33.9	36.0	36.9	35.8	39.1	34.2	37.8
2. R.W.	43.2	39.6	40.9	40.6	37.5	40.1	36.1	36.8				
3. L.S.	40.1	40.5	38.8	42.9	33.4	34.9	31.5	33.9			34.0	32.7
4. T.D.	38.3	36.4	40.6	41.1	37.5	37.4	41.3	37.4	39.3	40.1		
5. N.G.	43.1	43.0	40.1	42.0	41.8	41.4	37.6	41.0	36.1	36.2	37.8	37.7
6. E.T.	38.6	37.7	44.4	49.2	43.9	49.4	41.1	41.4	36.8	39.2	34.3	35.1
7. J.W.	42.3	41.2	40.8	41.0	36.6	39.8	39.1	41.6	36.9	39.5	34.1	34.6
8. J.D.	48.4	44.6	46.7	46.7	48.3	49.6	45.8	48.0	41.3		44.5	42.9
9. K.W.	34.1	35.0	34.4	34.3	30.9	31.5	30.1	32.6	28.8	27.4	32.6	31.2
10. S.H.	42.7	42.3	39.2	41.6	39.6	41.1						
MEAN	41.0	39.7	40.4	41.7	38.1	39.9	37.6	38.8	36.4	36.9	35.9	36.0
SD	3.85	3.13	3.40	4.14	5.59	6.02	4.92	4.69	3.90	4.86	4.10	3.88
N	10	10	10	10	10	10	9	9	7	6	7	7
	$2P < 0.05$		$2P < 0.05$		$2P < 0.01$		$2P > 0.10$		$2P > 0.10$		$2P > 0.90$	

Air-breathing

Times	2P	Times	2P
Preop - 8hr	>0.40	8 - 22hr	<0.05
" -22hr	<0.05	8 - 28hr	<0.01
" -28hr	<0.05	8 - 48hr	<0.005
" -48hr	<0.02	22 - 28hr	>0.80
" 10 days	<0.001	28 - 48hr	<0.01
		48hr-10days	>0.80

O_2-breathing

Times	2P	Times	2P
Preop - 8hr	>0.10	8 - 22hr	>0.05
" -22hr	>0.90	8 - 28hr	<0.05
" -28hr	>0.50	8 - 48hr	>0.05
" -48hr	>0.40	22 - 28hr	>0.40
" -10days	<0.02	28 - 48hr	>0.30
		48hr-10days	>0.50

Table 21. Arterial pH.

Subject	Preop Air	Preop O_2	8 hr Air	8 hr O_2	22 hr Air	22 hr O_2	28 hr Air	28 hr O_2	48 hr Air	48 hr O_2	10 days Air	10 days O_2
1. H.L.	7.442	7.462	7.418	7.423	7.462	7.462	7.468	7.473	7.498	7.478	7.476	7.441
2. R.W.	7.434	7.454	7.448	7.453	7.523	7.508	7.563	7.573				
3. L.S.	7.443	7.448	7.422	7.397	7.502	7.472	7.503	7.498			7.453	7.493
4. T.D.	7.390	7.420	7.427	7.452	7.516	7.541	7.410	7.500	7.449	7.454		
5. N.G.	7.457	7.457	7.453	7.443	7.469	7.489	7.476	7.456	7.487	7.477	7.501	7.506
6. E.T.	7.412	7.410	7.420	7.405	7.444	7.417	7.456	7.456	7.509	7.479	7.481	7.486
7. J.W.	7.401	7.409	7.452	7.447	7.466	7.448	7.447	7.437	7.511	7.486	7.461	7.461
8. J.D.	7.366	7.401	7.407	7.407	7.425	7.430	7.444	7.434	7.463		7.435	7.445
9. K.W.	7.404	7.419	7.458	7.453	7.517	7.512	7.505	7.490	7.500	7.500	7.491	7.506
10. S.H.	7.416	7.431	7.395	7.373	7.439	7.433						
MEAN	7.417	7.431	7.430	7.425	7.476	7.471	7.475	7.480	7.488	7.479	7.471	7.477
SD	0.028	0.023	0.022	0.029	0.036	0.041	0.045	0.043	0.024	0.015	0.023	0.028
N	10	10	10	10	10	10	9	9	7	6	7	7
	2P < 0.005		2P > 0.30		2P > 0.40		2P > 0.60		2P > 0.05		2P > 0.5	

Air-breathing

Times	2P	Times	2P
Pre - 8 hr	>0.10	8 - 22 hr	<0.001
" - 22 hr	<0.005	22 - 28 hr	>0.60
" - 28 hr	<0.005	28 - 48 hr	<0.02
" - 48 hr	<0.001	48 - 10days	>0.05
" - 10 days	<0.005		

O_2-breathing

Times	2P	Times	2P
Pre - 8 hr	>0.6	8 - 22 hr	<0.001
" - 22 hr	<0.02	22 - 28 hr	>0.70
" - 28 hr	<0.005	28 - 48 hr	>0.40
" - 48 hr	<0.01	48hr-10days	>0.70
" - 10 days	<0.02		

Arterial PO_2 and alveolar PO_2

Arterial PO_2 breathing air became significantly lower than the preoperative value at 22 hr and was lowest at 28 hr. By 10 days it had returned to the preoperative level. The lowest recorded PaO_2 was 44.8 mm Hg but mean values were greater than 60 mm Hg at all times. Reduction in O_2-breathing PaO_2 was significant 8 hr after operation and greatest at the time of the 48 hr study. The O_2-breathing PaO_2 had also returned to the preoperative level 10 days after operation. Mean values with 95%-confidence intervals of PaO_2 breathing air and O_2 are plotted in figure 13 (page 169).

Mean values and individual values of PAO_2 are shown in table 23. Air-breathing PAO2 rose after operation, reflecting the increase in alveolar ventilation; this persisted at the 10-day study.

Table 22. Arterial oxygen tension (mm Hg).

Subject	Preop		8 hr		22 hr		28 hr		48 hr		10 days	
	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2
1. H.L.	71.8	557	72.8	426	71.4	402	72.9	369	68.6	364	79.9	588
2. R.W.	78.1	594	49.7	555	44.8	324	48.2	325				
3. L.S.	70.4	492	66.0	452	63.8	353	54.2	358	56.7		69.9	575
4. T.D.	90.3	483	73.7	412	64.1	316	64.2	303	58.1	168		
5. N.G.	53.3	511	62.6	515	65.0	492	64.8	477	64.1	448	72.0	599
6. E.T.	79.9	531	60.9	312	50.7	207	52.7	235	61.9	341	66.9	448
7. J.W.	77.7	544	72.1	399	63.6	312	63.7	324	61.1	337	76.6	537
8. J.D.	72.7	597	75.0	523	70.6	458	73.6	409	67.9		65.6	529
9. K.W.	63.3	424	62.8	368	58.1	306	60.3	272	58.4	226	73.4	499
10. S.H.	70.4	524	70.8	511	68.9	442						
MEAN	72.8	526	66.6	447	62.1	361	61.6	341	62.1	314	72.0	539
SD	9.95	52.27	7.86	77.90	8.61	86.55	8.72	72.61	4.47	100.77	5.11	53.67
N	10	10	10	10	10	10	9	9	8	6	7	7

Air-breathing

Times	2P	Times	2P
Pre - 8 hr	>0.10	8 - 22 hr	<0.01
" - 22 hr	<0.05	22 - 28 hr	>0.80
" - 28 hr	<0.05	28 - 48 hr	>0.50
" - 48 hr	>0.05	48 - 10days	<0.01
" - 10days	>0.60		

O_2-breathing

Times	2P	Times	2P
Pre - 8 hr	<0.01	8 - 22 hr	<0.005
" - 22 hr	<0.001	22 - 28 hr	>0.20
" - 28 hr	<0.001	28 - 48 hr	>0.60
" - 48 hr	<0.005	48hr-10days	<0.005
" - 10days	>0.50		

Table 23. Alveolar oxygen tension (mm Hg)

Subject	Preop		8 hr		22 hr		28 hr		48 hr		10 days	
	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2
1. H.L.	94.9	670	95.9	671	108	676	99.3	673	101	670	105	672
2. R.W.	92.1	660	101	659	102	663	105	666				
3. L.S.	99.8	672	105	666	107	652	109	674	115		103	667
4. T.D.	99.2	677	92.9	668	98.7	672	89.6	670	93.4	664		
5. N.G.	83.6	664	102	665	93.8	658	100	654	98.5	652	97.6	662
6. E.T.	97.6	658	91.9	655	94.3	653	94.7	659	99.9	661	103	671
7. J.W.	94.2	668	99.8	658	103	660	97.8	658	98.7	659	96.9	666
8. J.D.	81.1	657	87.2	653	87.1	650	88.7	652	95.2		89.1	661
9. K.W.	101	674	103	669	108	673	107	675	111	680	102	682
10. S.H.	91.3	658	99.2	659	99.0	662						
MEAN	93.5	666	97.8	662	100	662	99.0	665	102	664	99.5	669
SD	6.72	7.38	5.65	6.27	6.94	9.21	7.21	8.97	7.54	9.69	5.47	7.16
N	10	10	10	10	10	10	9	9	8	6	7	7

Air-breathing

Times	2P	Times	2P
Pre - 8 hr	>0.05	8 - 22 hr	>0.10
" - 22 hr	<0.005	22 - 28 hr	>0.50
" - 28 hr	>0.05	28 - 48 hr	<0.02
" - 48 hr	<0.05	48 - 10days	>0.20
" - 10 days	<0.02		

O_2-breathing

Times	2P	Times	2P
Pre - 8 hr	<0.025	8 - 22 hr	>0.80
" - 22 hr	>0.10	22 - 28 hr	>0.30
" - 28 hr	>0.30	28 - 48 hr	>0.70
" - 48 hr	>0.20	48hr-10days	<0.05
" - 10 days	>0.30		

Physiological dead space

Comparing measured values of V_D from one occasion to another is difficult because of the influence of other variables on V_D. Harris et al. (1973) derived a prediction equation for V_D which allows for the influence of age, height, V_T and f:

$$V_D = 0.93 \text{ Age} - 1.725 \text{ Ht} - 0.267 V_T - 1291/f - 213.$$

Expressing measured V_D as a percentage of the V_D predicted from this equation to some degree normalises the value for differences in these variables. In table 24, individual and mean values of V_D are shown. No worthwhile comparison between different times or between air- and O_2-breathing periods can be made from these values as there are concomitant changes in V_T and f. To improve the comparisons each value of V_D has been expressed as a percentage of the V_D calculated, with the appropriate V_T and f, from the above equation. The means and standard deviation of these percentages (V_D%) are also shown in table 24. Air- and O_2-breathing values of V_D% were significantly different on two occasions so for all times air- and O_2-breathing V_D%s have been analysed separately. The P values in the table apply only to V_D%s. The means of all measured V_Ds on air was 150 ml and on O_2 was 158 ml, ($2P < 0.005$). From the prediction equation, it seemed that only about 1 ml of this could be explained by the change in V_T and f.

Breathing air V_D% was smaller than preoperatively at all times after operation. The decreases were significant except at 10 days. The O_2-breathing V_D% followed the same pattern of change. It fell soon after operation (significant only at 28 hr) and then rose again, and in fact was bigger than the preoperative V_D at 10 days.

Table 24. Physiological dead-space (ml).

Subject	Preop Air	Preop O_2	8 hr Air	8 hr O_2	22 hr Air	22 hr O_2	28 hr Air	28 hr O_2	48 hr Air	48 hr O_2	10 days Air	10 days O_2
1. H.L.	154	165	123	136	156	184	129	157	149	170	213	209
2. R.W.	87.0	88.0	94.6	95.0	98.5	108	118	124				
3. L.S.	181	158	175	168	175	170	140	157			130	121
4. T.D.	127	139	118	126	102	128	99.6	116	95.9	133		
5. N.G.	115	122	113	167	92.0	137	123	163	123	138	162	209
6. E.T.	169	176	200	162	188	177	167	180	208	219	200	204
7. J.W.	187	180	164	158	168	176	143	155	154	159	158	221
8. J.D.	154	169	194	150	156	165	144	142	154		141	141
9. K.W.	150	184	159	176	174	173	166	183	208	200	181	205
10. S.H.	132	136	174	168	156	146						
MEAN	146	152	151	151	147	156	137	153	156	170	169	187
SD	30.9	30.4	36.6	25.0	35.4	25.3	21.9	22.6	41.2	34.1	30.3	39.2
N	10	10	10	10	10	10	9	9	7	6	7	7
V_D expressed as % of V_D predicted for age, height, V_T and f, (minus 12.5% for lying position)												
MEAN	122	115	106	109	101	110	96.1	105	104	113	113	123
SD	19.4	18.1	16.7	15.5	16.2	17.6	14.0	14.5	17.2	15.6	12.4	22.7
	2P > 0.05		2P > 0.40		2P < 0.005		2P <0.05		2P>0.05		2P >0.05	

Air-breathing Times	2P
Preop - 8 hr	<0.02
" - 22 hr	<0.005
" - 28 hr	<0.005
" - 48 hr	<0.05
" - 10 days	>0.05

O_2-breathing Times	2P
Preop - 8 hr	>0.20
" - 22 hr	>0.30
" - 28 hr	<0.05
" - 48 hr	>0.10
" - 10 days	>0.80

Functional residual capacity

Table 25 shows individual and mean values of FRC calculated from the nitrogen washout traces (see calculation and discussion). Only five of the patients completed analyzable curves at all studies and their results have been considered both separately and with the rest of the group in looking for significant differences.

FRC fell progressively after operation and was lowest during the 48 hr study. By 10 days the FRC had returned to the preoperative level. None of these differences was, however, significant by paired t-test.

Relative Ventilation Ratio and Index of Alveolar Ventilation

The RVR and IAV were used as measures of the evenness of distribution of inspired gas. There was little difference between the preoperative and 10 day-postoperative values (table 26). After the 8 hr study it appeared that distribution became more even as RVR fell (significantly at 28 hr) and IAV rose. Two patients do not follow the mean pattern. Subjects 8 and 9 had the lowest RVRs and highest IAVs before operation both showed a rise in RVR and a fall in IAV after the operation. Abnormal indices before operation are marked with an asterisk.

Table 25. FUNCTIONAL RESIDUAL CAPACITY (ml)

Subject	Preop.	8 hr	22 hr	28 hr	48 hr	10 days
1. H.L.	2960	3580	1960	1670	1150	1885
2. R.W.	1860	1200	922	1270		
3. L.S.	2300	3580	3500	3250		3790
4. T.D.	1610	2000	2000	1370	1410	
5. N.G.	2400	2030	1670	1650	2420	2650
6. E.T.	2050	1180	950	1720	2080	1460
7. J.W.	1454	1510	1680	1600	1560	2070
8. J.D.	3480	2660	2910	2130		3110
9. K.W.	1910	1680	1520	1240	917	1840
10. S.H.	1903	2223		1730		
MEAN	2193	2164	1901	1763	1590	2401
SD	621.9	873.3	844.0	583.8	567.2	823.6
N	10	10	9	10	6	7

All subjects

Times	2P	Times	2P
Preop. - 8 hr	>0.80	8 - 22 hr	>0.10
" - 22 hr	>0.20	22 - 28 hr	>0.40
" - 28 hr	>0.05	28 - 48 hr	>0.80
" - 48 hr	>0.10	48 - 10days	>0.20
" - 10 days	>0.90		

5 Complete

Times	2P	Times	2P
Preop. - 8 hr	>0.50	22 - 28 hr	>0.90
" -22 hr	>0.05	48 - 10days	>0.20
" -28 hr	>0.05		
" -48 hr	>0.20		
" -10days	>0.50		

Table 26.

Subject	RELATIVE VENTILATION RATIO						INDEX OF ALVEOLAR VENTILATION					
	Preop.	8 hr	22 hr	28 hr	48 hr	10 days	Preop.	8 hr	22 hr	28 hr	48 hr	10 days
1. H.L.	6.34	18.0	5.85	6.97	5.80	5.82	43.0	54.9	36.2	31.0	34.0	33.3
2. R.W.	5.01	6.05	4.20	3.20			48.3	76.4	39.8	55.8		
3. L.S.	5.41	6.06	3.01	5.13		3.57	30.9*	50.4	62.0	44.9		52.0
4. T.D.	11.8*	11.2	5.38	3.21	2.95		50.5	74.0	73.3	58.6	60.2	
5. N.G.	8.51*	9.14	9.86	3.26	3.20	7.58	25.9*	33.0	19.2	53.2	50.3	33.3
6. E.T.	5.16	9.54	7.18	4.36	5.13	7.81	36.0*	28.9	26.4	44.1	38.0	28.1
7. J.W.	10.6*	5.56	3.78	3.86	4.52	7.65	17.2*	30.7	46.1	47.5	39.9	25.4
8. J.D.	3.70	4.83	5.26	4.00		4.45	55.0	53.7	59.1	42.8		43.6
9. K.W.	3.23	4.97	4.06	4.54	6.82	6.53	53.1	39.3	56.5	39.8	37.0	48.2
10. S.H.	9.06*	4.74		4.87			20.6*	14.5		62.8		
MEAN	6.89	8.01	5.40	4.34	4.74	6.20	38.0	45.6	46.5	48.0	43.2	37.7
SD	2.95	4.19	2.09	1.15	1.50	1.67	13.9	20.0	17.7	9.59	10.0	10.3
N	10	10	9	10	6	7	10	10	9	10	6	7

Times	2P	Times	2P
Preop - 8 hr	>0.40	8 - 22 hr	>0.05
" -22 hr	>0.20	22 - 28 hr	>0.20
" -28 hr	<0.05	28 - 48 hr	>0.40
" -48 hr	>0.10	48hr-10days	>0.05
" -10 days	>0.90		

Times	2P	Times	2P
Preop - 8 hr	>0.10	8 - 22 hr	>0.60
" - 22 hr	>0.20	22 - 28 hr	>0.98
" - 28 hr	>0.10	28 - 48 hr	>0.20
" - 48 hr	>0.40	48hr-10days	>0.20
" - 10days	>0.90		

* Abnormal preoperative value.

$\Delta AaPO_2$ after CPBP

Table 27 shows individual and mean values for $\Delta AaPO_2$ breathing air and O_2 before and after operation. The asterisk marks the one value preoperatively that is outside, the very wide 95%-confidence intervals for $\Delta AaPO_2$ in the group of "normals" (figure 5, part I).

Both air- and O_2-breathing $\Delta AaPO_2$ were increased 8 hr after operation and rose progressively to the 48-hr study. Ten days after operation air-breathing and O_2-breathing $\Delta AaPO_2$ were not significantly different from the preoperative values.

The patients who had the highest $\Delta AaPO_2$s at 48 hr were those who had the highest preoperatively ($r = 0.6875$, $2P < 0.05$) for air breathing), but the correlation of preoperative $\Delta AaPO_2$ with post-operative $\Delta AaPO_2$ was not significant at any of the other times.

Table 27. ALVEOLAR TO ARTERIAL OXYGEN TENSION DIFFERENCE (mm Hg)

Subject	Preop.		8 hr		22 hr		28 hr		48 hr		10 days	
	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2
1. H.L.	23.1	113	23.1	245	36.9	274	26.4	304	32.5	306	25.3	84.2
2. R.W.	14.0	66.5	51.6	104	57.0	339	56.3	341				
3. L.S.	29.4	180	38.5	214	43.5	299	54.7	316	58.5		32.7	92.3
4. T.D.	8.90	194	19.2	256	34.6	356	25.4	367	35.3	496		
5. N.G.	30.3	153	39.3	150	28.8	166	35.3	177	34.4	204	25.6	63.1
6. E.T.	17.7	127	31.0	343	43.6	447	42.0	424	38.0	320	36.3	223
7. J.W.	16.5	124	27.7	259	39.2	348	34.1	334	37.6	322	20.3	129
8. J.D.	8.40	60.2	12.2	130	16.5	192	15.1	243	27.3		23.5	132
9. K.W.	37.8	250*	40.0	301	49.9	367	47.1	403	52.6	454	28.8	183
10. S.H.	20.9	134	28.4	148	30.1	220						
MEAN	20.7	140	31.1	215	38.0	301	37.4	323	39.5	350	27.5	130
SD	9.59	57.5	11.6	79.3	11.5	88.0	13.9	76.7	10.6	107	5.52	56.9
N	10	10	10	10	10	10	9	9	8	6	7	7

Air-breathing

Times	2P	Times	2P
Preop - 8 hr	<0.02	8 - 22 hr	<0.02
" - 22 hr	<0.005	22 - 28 hr	>0.50
" - 28 hr	<0.005	28 - 48 hr	<0.05
" - 48 hr	<0.001	48 - 10 days	<0.02
" - 10 days	>0.20		

O_2-breathing

Times	2P	Times	2P
Preop - 8 hr	<0.01	8 - 22 hr	<0.005
" -22 hr	<0.001	22 - 28 hr	>0.10
" -28 hr	<0.001	28 - 48 hr	>0.60
" -48 hr	<0.005	48hr-10days	<0.005
" -10 days	>0.60		

* Abnormal preoperative value.

$\dot{Q}_{Va}/\dot{Q}_t$ after CPBP

Table 28 shows individual and mean values for air- and O_2-breathing venous admixture. Of the preoperative admixtures only one was outside the 95%-confidence interval for the "normal" group (figure 7, part I). There was little difference between air- and O_2-breathing venous admixtures. The only time at which the differences were significant was at 48 hr when the admixture during O_2-breathing was bigger than when air was breathed. The mean differences between air- and O_2-breathing admixture were successively +2.57, +1.3, +0.7, -0.59, -2.9 and +1.29%.

Air-breathing admixture was increased above the preoperative level in the early postoperative studies. It was biggest at 22 hr but was below the preoperative level at the 10-day study. Only the drop between 48 hr and 10 days was a statistically significant change. The postoperative increases in O_2-breathing admixture were bigger than when air was breathed, largest at 48 hr, and always significantly different from the preoperative value. By the 10-day study O_2-breathing admixture was virtually the same as preoperatively. For all measurements air- and O_2-breathing admixtures were closely correlated ($r = 0.6138$, $2P < 0.001$). For all measurements both air- and O_2-breathing $\dot{Q}_{Va}/\dot{Q}_t$ were closely correlated with their respective PaO_2s and $\Delta AaPO_2$s ($r = -0.8465, -0.9423, 0.6487, 0.9427$; all $2P < 0.001$).

For all values of venous admixture the actual postoperative change was correlated with the percentage change in FRC ($r = -0.2262$ $2P < 0.05$). For O_2-breathing admixture alone r rose to -0.495, $2P < 0.01$, and for air-breathing admixture only $r = 0.1380$, $2P > 0.1$.

The correlation between preoperative $\dot{Q}_{Va}/\dot{Q}_t$ and postoperative

Table 28. VENOUS ADMIXTURE (percentage of cardiac output).

Subject	Preop. Air	Preop. O_2	8 hr Air	8 hr O_2	22 hr Air	22 hr O_2	28 hr Air	28 hr O_2	48 hr Air	48 hr O_2	10 days Air	10 days O_2
1. H.L.	9.81	6.35	11.09	13.08	9.31	11.23	8.14	15.33	10.81	14.50	5.90	4.30
2. R.W.	5.49	3.72	16.38	3.76	19.47	11.71	14.18	11.31				
3. L.S.	9.79	8.71	10.47	10.11	10.91	12.52	17.35	13.98	12.08		9.05	3.88
4. T.D.	2.09	8.92	6.28	11.19	9.25	13.33	13.18	14.90	16.45	19.14		
5. N.G.	20.54*	6.95	14.71	5.38	8.85	6.62	9.12	6.04	8.18	7.40	7.29	3.34
6. E.T.	6.81	6.21	19.64	19.56	29.33	22.15	23.77	20.33	13.73	16.64	10.59	12.87
7. J.W.	7.20	6.37	10.22	14.36	12.94	14.29	14.60	15.12	13.28	15.31	4.80	6.80
8. J.D.	5.82	3.58	7.36	8.43	9.58	11.15	7.76	13.22	11.16		13.00	8.10
9. K.W.	17.00	11.80	14.17	14.73	14.98	16.20	14.50	17.62	16.81	21.28	7.90	10.20
10. S.H.	11.31	7.57	10.37	7.14	12.48	10.91						
MEAN	9.59	7.02	12.07	10.77	13.71	13.01	13.62	14.21	12.81	15.71	8.36	7.07
SD	5.56	2.45	4.12	4.82	6.40	4.07	5.05	4.00	2.90	4.78	2.80	3.57
N	10	10	10	10	10	10	9	9	8	6	7	7
	2P> 0.10		2P > 0.40		2P > 0.50		2P > 0.60		2P < 0.02		2P > 0.30	

Air-breathing

Times	2P	Times	2P
Preop. - 8 hr	>0.20	8 - 22 hr	>0.20
" - 22 hr	>0.10	22 - 28 hr	>0.80
" - 28 hr	>0.10	28 - 48 hr	>0.60
" - 48 hr	>0.30	48 - 10days	<0.05
" - 10days	>0.30		

O_2-breathing

Times	2P	Times	2P
Preop. - 8 hr	<0.05	8 - 22 hr	<0.025
" - 22 hr	<0.005	22 - 28 hr	>0.10
" - 28 hr	<0.001	28 - 48 hr	>0.50
" - 48 hr	<0.005	48 - 10days	<0.01
" - 10days	>0.95		

* Abnormal preoperative value.

$\dot{Q}_{Va}/\dot{Q}_t$ did not approach a significant level at any of the studies, suggesting that the patients with big admixtures before operation did not necessarily have the biggest admixtures after operation. This may be demonstrated in another way. The absolute change in $\dot{Q}_{Va}/\dot{Q}_t$ between the preoperative study and each postoperative study was calculated, and then at each postoperative stage this change was correlated with the preoperative value. The results are as follows:

Postoperative stage	Correlation between Preoperative $\dot{Q}_{Va}/\dot{Q}_t$ and $\Delta\dot{Q}_{Va}/\dot{Q}_t$	
	Air	O_2
22 hr	-0.7368 (2P < 0.01)	-0.5607 (2P > 0.05)
28 hr	-0.8151 (2P < 0.01)	-0.6485 (2P > 0.05)
48 hr	-0.9363 (2P < 0.001)	-0.7433 (2P > 0.05)

The change in air-breathing $\dot{Q}_{Va}/\dot{Q}_t$ is negatively correlated with the preoperative value; that is, the higher the initial value the less change occurred. For O_2-breathing also, correlations were negative but did not quite reach significance.

Of the preoperative data listed in table 15 only the supine value for CV-ERV is significantly correlated with the preoperative value of venous admixture (c.f. part I). Some of the correlations are shown below:

Preoperative data		Preoperative $\dot{Q}_{Va}/\dot{Q}_t$ AIR	O_2
Number of cigarettes/day	r	0.0387	-0.048
	2P	>>0.1	>>0.1
FEV_1/VC % NORMAL	r	0.2389	0.2906
	2P	>>0.1	>>0.1
Supine CV-ERV	r	0.7941	0.7990
	2P	<0.01	<0.01
CV/VC % NORMAL	r	0.563	0.335
	2P	>0.05	>0.1
LVEDP	r	-0.4066	0.2188
	2P	>>0.1	>>0.1
Ejection fraction %	r	-0.273	0.224
	2P	>>0.1	>>0.1

Correlations have been sought between preoperative and operative data and the change in $\dot{Q}_{Va}/\dot{Q}_t$ after operation. The absolute change of $\dot{Q}_{Va}/\dot{Q}_t$ has been used (postoperative $\dot{Q}_{Va}/\dot{Q}_t$ - preoperative $\dot{Q}_{Va}/\dot{Q}_t$). As the maximum changes occured around 28 - 48 hr the average of the changes at these two times has been used as an index of postoperative change, air- and O_2-breathing values being analysed separately. The postoperative change in air-breathing $\dot{Q}_{Va}/\dot{Q}_t$ was significantly correlated with the postoperative change in O_2-breathing $\dot{Q}_{Va}/\dot{Q}_t$ ($r = 0.765$, $2P < 0.01$). Some of the correlations with preoperative and operative data are shown in table 29.

Supine CV-ERV and CV/VC ratio are negatively correlated with the postoperative change in $\dot{Q}_{Va}/\dot{Q}_t$ (significant only with the change in air-breathing admixture). None of the other operative or preoperative data seems to be a useful predictor of the postoperative change.

Table 29. CORRELATION OF OPERATIVE AND PREOPERATIVE DATA WITH THE POSTOPERATIVE CHANGE OF $\dot{Q}va/\dot{Q}t$.

	Postoperative change of $\dot{Q}va/\dot{Q}t$			
	Air		O_2	
	r	2P	r	2P
NUMBER OF CIGARETTES PER DAY	-0.1547	N.S.	0.0686	N.S.
FEV_1/VC % NORMAL	-0.2517	N.S.	0.1092	N.S.
SUPINE CV - ERV	-0.6519	<0.05	-0.4749	N.S.
CV/VC % NORMAL	-0.6450	<0.05	-0.4683	N.S.
SRaw	-0.2870	N.S.	0.0338	N.S.
LVEDP	0.4398	N.S.	0.0144	N.S.
EJECTION FRACTION %	0.6272	N.S.	0.5318	N.S.
OPERATION TIME	-0.3097	N.S.	-0.1425	N.S.
BYPASS TIME	-0.2288	N.S.	0.0801	N.S.
X-MATCH BLOOD (1.)	-0.1464	N.S.	-0.3472	N.S.

LVEDP, left ventricular end diastolic pressure (mm Hg),

N.S., not significant.

Oxygen uptake and respiratory quotient

Individual and mean values for $\dot{V}_{O_2}$ and R are shown in tables 30 and 31. $\dot{V}_{O_2}$ became significantly higher than preoperatively 22 hr after the operation and remained elevated at the 10 day study. Mean oral temperatures were 36.5, 37.1, 37.2, 37.2, and 36.8°C at the preoperative, 8 hr, 22 hr, 28 hr, 48 hr, and 10 day studies respectively.

Table 30. OXYGEN UPTAKE (ml. min^{-1}).

Subject	Preop.	8 hr	22 hr	28 hr	48 hr	10 days
1. H.L.	262	267	283	292	280	299
2. R.W.	214	233	240	243		
3. L.S.	199	179	222	243	230	218
4. T.D.	235	237	261	294	234	
5. N.G.	143	127	158	216	218	169
6. E.T.	229	281	230	201	258	262
7. J.W.	215	242	247	247	260	245
8. J.D.	189	249	234	250	268	220
9. K.W.	172	214	212	250	251	238
10. S.H.	233	231	259			
MEAN	209	226	235	248	250	236
SD	34.6	44.5	34.0	30.3	20.9	40.4
N	10	10	10	9	8	7

Times	2P	Times	2P
Preop - 8 hr	>0.05	8 - 22 hr	>0.30
" - 22 hr	<0.001	22 - 28 hr	>0.05
" - 28 hr	<0.005	28 - 48 hr	>0.95
" - 48 hr	<0.05	48hr-10days	>0.10
" - 10days	<0.001		

Table 31. RESPIRATORY GAS EXCHANGE RATIO.

Subject	Preop.	8 hr	22 hr	28 hr	48 hr	10 days
1. H.L.	0.683	0.659	0.714	0.673	0.702	0.736
2. R.W.	0.744	0.870	0.780	0.803		
3. L.S.	0.764	0.856	0.763	0.750	0.800	0.720
4. T.D.	0.712	0.676	0.700	0.650	0.673	
5. N.G.	0.610	0.830	0.748	0.784	0.742	0.746
6. E.T.	0.755	0.764	0.803	0.759	0.747	0.739
7. J.W.	0.738	0.835	0.792	0.762	0.754	0.631
8. J.D.	0.692	0.753	0.778	0.767	0.789	0.713
9. K.W.	0.664	0.722	0.732	0.680	0.725	0.634
10. S.H.	0.725	0.804	0.793			
MEAN	0.709	0.777	0.760	0.736	0.741	0.703
SD	0.047	0.074	0.035	0.054	0.042	0.049
N	10	10	10	9	8	7

Times	2P	Times	2P
Preop - 8 hr	<0.02	8 - 22 hr	>0.30
" - 22 hr	<0.005	22 - 28 hr	>0.05
" - 28 hr	>0.20	28 - 48 hr	>0.20
" - 48 hr	>0.05	48hr-10days	>0.05
" - 10days	>0.90		

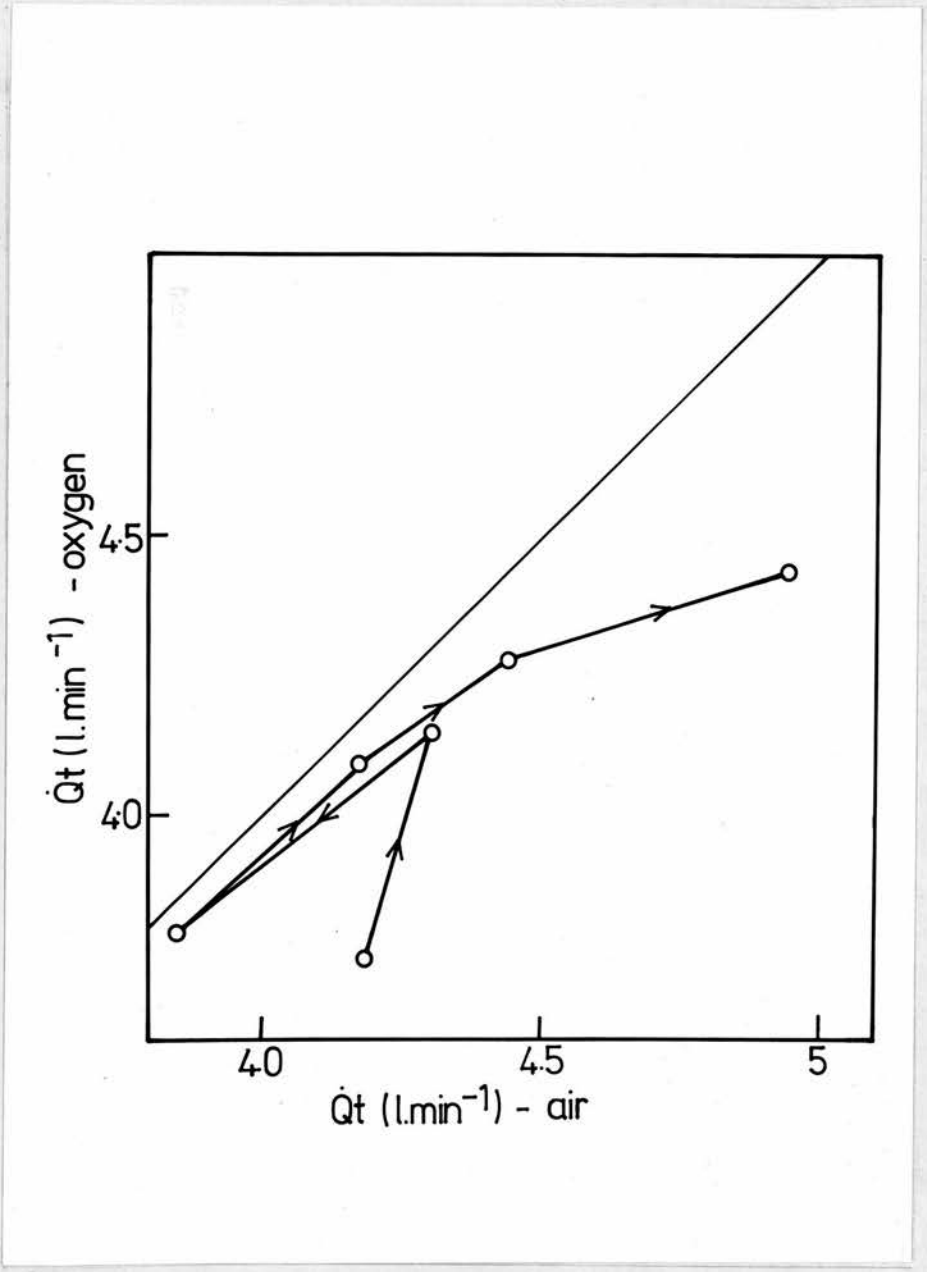


Figure 12. Mean values, for all subjects, of cardiac output while breathing air plotted against cardiac output while breathing O_2. Following the direction of the arrows the mean value properatively and at 8, 22, 28, 48 hr and 10 days after operation is indicated. The line of identity is shown.

Cardiac output and arterio-venous O_2-content difference

Individual and mean values are shown in tables 32 and 33. The asterisks at the 8 hr study indicate two patients who had atrial pacing at that time. The asterisk at the 48 hr study indicates a patient who was in atrial fibrillation at that time. All other measurements were with the subjects in sinus rhythm.

Cardiac output was lower and therefore $\Delta a\bar{v}C_{O_2}$ higher when O_2 was breathed than when air was breathed. These differences were significant preoperatively, became insignificant in the early postoperative period, and were significant again at the 48 hr and 10-day studies (see figure 12). For cardiac output when breathing air only the 10-day values was significantly different from the preoperative level. Cardiac output fell a little 22-28 hr after the operation and then rose to above the preoperative value at 48 hr and 10 days. Cardiac output breathing O_2 was higher than preoperatively at all times after operation, lowest at 22-28 hr, and significantly higher than preoperatively only at 10 days.

Both air- and O_2-breathing $\Delta a\bar{v}C_{O_2}$ were increased above the preoperative level at all times up to 48 hr after operation. By 10 days both were slightly lower than preoperatively. Arterio-venous oxygen content difference on air was closely related to $\Delta a\bar{v}C_{O_2}$ when oxygen was breathed r 0.8635, $2P < 0.001$. The preoperative value of $\Delta a\bar{v}C_{O_2}$ was significantly correlated with postoperative $\Delta a\bar{v}C_{O_2}$ at 48 hr and 10 days $r = 0.562$, $2P < 0.05$, $r = 0.4995$, $2P < 0.05$ respectively.

Table 32. CARDIAC OUTPUT (l. min^{-1}).

Subject	Preop. Air	Preop. O_2	8 hr Air	8 hr O_2	22 hr Air	22 hr O_2	28 hr Air	28 hr O_2	48 hr Air	48 hr O_2	10 days Air	10 days O_2
1. H.L.	5.85	5.04	5.95	5.29	4.47	4.16	4.88	5.63	5.38	5.00	5.61	5.24
2. R.W.	4.15	3.93	3.19	2.76	3.45	2.97	3.38	2.92				
3. L.S.	3.49	3.39	3.22*	3.05	3.53	3.42	4.02	4.03	3.07*		3.62	3.15
4. T.D.	3.87	3.83	3.53	3.78	3.60	3.61	4.75	4.47	3.63	3.38		
5. N.G.	2.72	2.27	2.30	1.57	2.10	2.20	2.82	2.53	3.04	2.72	3.35	3.08
6. E.T.	4.78	3.89	6.36	6.39	4.34	4.48	3.92	3.77	5.27	5.15	6.21	5.61
7. J.W.	4.27	3.75	4.83	5.07	3.99	3.78	4.54	4.23	5.20	4.70	4.57	4.47
8. J.D.	4.17	3.78	5.82	5.74	4.51	4.98	4.78	5.01	4.81		5.57	4.73
9. K.W.	3.33	2.95	4.06	3.89	3.93	3.56	4.46	4.24	5.12	4.74	5.67	4.84
10. S.H.	5.21	4.54	3.71*	3.95	4.62	4.73						
MEAN	4.18	3.74	4.30	4.15	3.85	3.79	4.17	4.09	4.44	4.28	4.94	4.45
SD	0.92	0.77	1.37	1.48	0.75	0.84	0.70	0.96	1.02	0.99	1.11	0.98
N	10	10	10	10	10	10	9	9	8	6	7	7
	2P < 0.001		2P > 0.20		2P > 0.40		2P > 0.50		2P < 0.005		2P < 0.005	

Air-breathing

Times	2P	Times	2P
Preop - 8 hr	>0.70	8 - 22 hr	>0.10
" - 22 hr	>0.05	22 - 28 hr	<0.025
" - 28 hr	>0.70	28 - 48 hr	>0.50
" - 48 hr	>0.20	48hr-10days	>0.05
" - 10 days	<0.05		

O_2-breathing

Times	2P	Times	2P
Preop - 8 hr	>0.30	8 - 22 hr	>0.20
" - 22 hr	>0.80	22 - 28 hr	>0.05
" - 28 hr	>0.05	28 - 48 hr	>0.70
" - 48 hr	>0.10	48hr-10days	>0.10
" - 10 days	<0.025		

* Subjects not in sinus rhythm.

Table 33. ARTERIO-VENOUS OXYGEN CONTENT DIFFERENCE (ml. 100 ml^{-1}).

Subject	Preop.		8 hr		22 hr		28 hr		48 hr		10 days	
	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2
1. H.L.	4.48	5.20	4.49	5.05	6.33	6.80	5.98	5.19	5.20	5.60	5.33	5.71
2. R.W.	5.16	5.44	7.30	8.45	6.95	8.07	7.20	8.31				
3. L.S.	5.71	5.87	5.56	5.87	6.29	6.50	6.05	6.03	7.50		6.03	6.93
4. T.D.	6.08	6.13	6.72	6.27	7.26	7.22	6.19	6.57	6.45	6.93		
5. N.G.	5.26	6.29	5.51	8.09	7.52	7.19	7.67	8.55	7.18	8.01	4.83	5.49
6. E.T.	4.79	5.89	4.42	4.40	5.30	5.13	5.13	5.33	4.90	5.01	4.22	4.67
7. J.W.	5.03	5.73	5.01	4.77	6.19	6.54	5.44.	5.84	5.00	5.53	5.36	5.48
8. J.D.	4.53	5.00	4.28	4.34	5.19	4.70	5.23	4.99	5.57		3.95	4.65
9. K.W.	5.17	5.83	5.27	5.50	5.39	5.95	5.60	5.89	4.90	5.29	4.20	4.92
10. S.H.	4.47	5.13	6.22	5.85	5.61	5.47						
MEAN	5.07	5.65	5.48	5.86	6.20	6.36	6.05	6.30	5.84	6.06	4.85	5.41
SD	0.53	0.44	1.01	1.42	0.84	1.04	0.87	1.30	1.06	1.16	0.77	0.79
N	10	10	10	10	10	10	9	9	8	6	7	7
	2P < 0.001		2P > 0.20		2P > 0.20		2P > 0.20		2P < 0.005		2P < 0.005	

Air-breathing				O_2-breathing			
Times	2P	Times	2P	Times	2P	Times	2P
Preop - 8 hr	>0.10	8 - 22 hr	<0.025	Preop - 8 hr	>0.60	8 - 22 hr	>0.10
" - 22 hr	<0.001	22 - 28 hr	>0.10	" - 22 hr	<0.05	22 - 28 hr	>0.50
" - 28 hr	<0.02	28 - 48 hr	>0.70	" - 28 hr	>0.10	28 - 48 hr	>0.30
" - 48 hr	<0.05	48hr-10days	<0.05	" - 48 hr	>0.60	48hr-10days	>0.20
" - 10days	>0.50			" - 10days	>0.30		

Correlations of the degree of change in $\Delta a\bar{v}C_{O_2}$ after operation with preoperative and operative factors were sought and are summarised in table 34. The same index of postoperative change has been used as with the $\dot{Q}_{Va}/\dot{Q}_t$ correlations i.e. mean value of postoperative minus preoperative $\Delta a\bar{v}C_{O_2}$ at 28 and 48 hr. Changes on air and O_2 have again been analysed separately although the postoperative change in air is closely correlated with the change when O_2 is breathed $r = 0.8497$, $2P < 0.01$. Only the preoperative left ventricular ejection fraction, the operation time and the bypass time approach a significant correlation.

Mean values of PaO_2, $\dot{Q}_{Va}/\dot{Q}_t$ and $\Delta a\bar{v}C_{O_2}$ at all studies are summarised graphically in figure 13.

Table 34. CORRELATION OF OPERATIVE AND PREOPERATIVE DATA WITH THE POSTOPERATIVE CHANGE OF $\Delta a\bar{v}C_{O_2}$.

	Postoperative change of $\Delta a\bar{v}C_{O_2}$			
	Air		O_2	
	r	2P	r	2P
PREOPERATIVE $\Delta a\bar{v}C_{O_2}$	-0.0548	N.S.	0.1070	N.S.
LVEDP	-0.2669	N.S.	0.0271	N.S.
EJECTION FRACTION %	-0.5146	N.S.	-0.2623	N.S.
OPERATION TIME	0.5246	N.S.	0.2521	N.S.
BYPASS TIME	0.4836	N.S.	0.3031	N.S.
AORTIC CLAMP TIME	0.1658	N.S.	0.0888	N.S.

LVEDP, left ventricular end-diastolic pressure (mm Hg),

N.S., not significant.

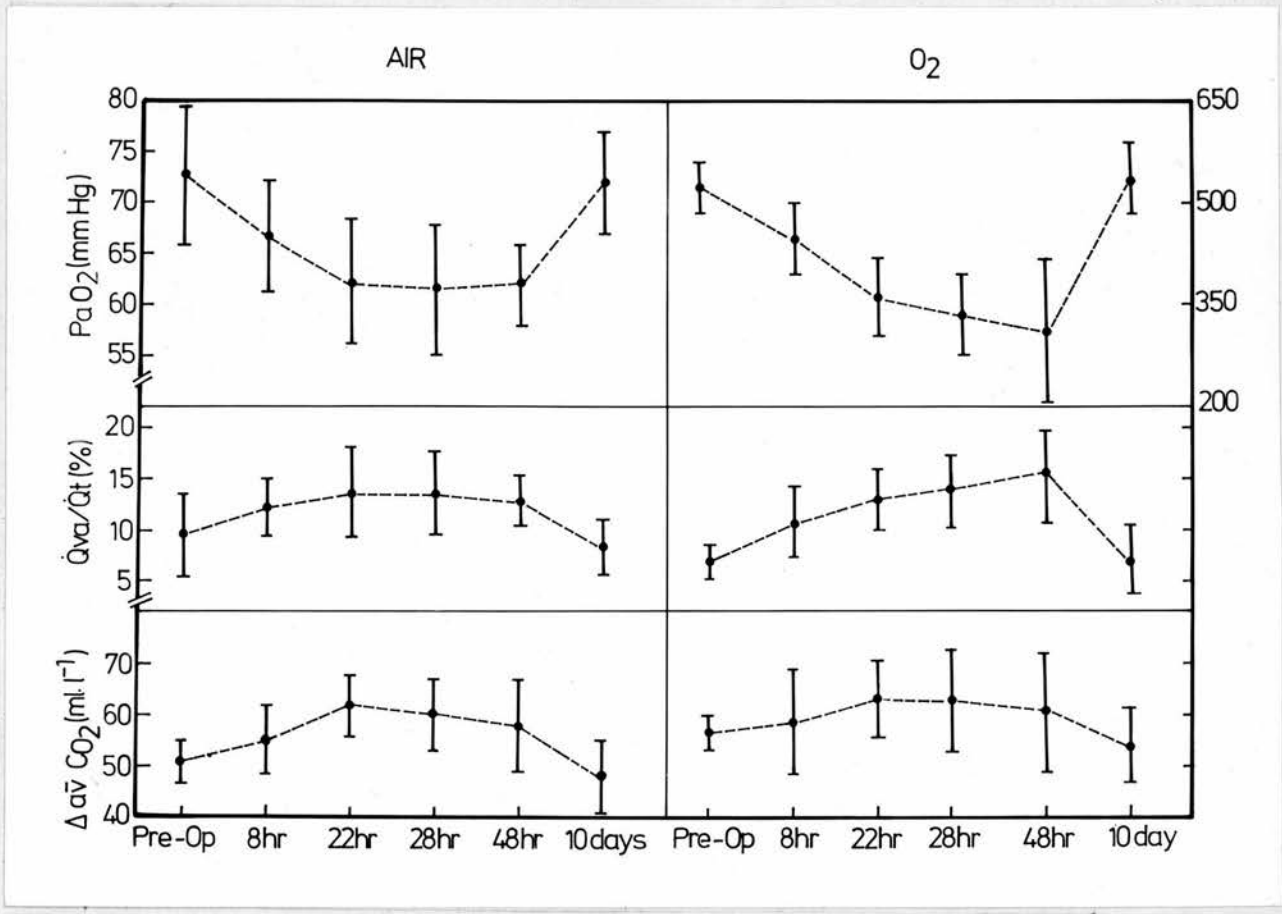


Figure 13. Mean values, for all subjects, of Pa_{O_2}, $\dot{Q}va/\dot{Q}t$ and $\Delta a\bar{v}C_{O_2}$, preoperatively and at each of the postoperative studies. The bars represent 95%-confidence intervals of the means.

Discussion

Ventilation

There was a highly significant increase in $\dot{V}_E$ immediately after operation, and this had not subsided by 10 days. The fall in $PaCO_2$ which accompanied this shows that there was alveolar hyperventilation in excess of the demand for CO_2 elimination. It is of interest to determine what the stimulus might have been for this overventilation. Since $PaCO_2$ was reduced, a CO_2 stimulus was not responsible. Nor was metabolic acidosis, since pH was raised during the whole of the postoperative period. The remaining chemical stimulus, hypoxia, is virtually excluded for two reasons: first, the arterial PO_2 was seldom less than 60 mm Hg in any patient, and was invariably above 65 mm Hg at 10 days, when hyperventilation was still present; secondly, breathing O_2 did not restore the preoperative ventilation at any stage after operation. Cortical overbreathing is unlikely since the time-course of overbreathing was so smooth and uniform. The most probable cause seems to be a reflex stimulus from lungs or thorax or both. During the first 36 hours, pain from the sternotomy is pronounced and is certain to have influenced breathing; but at 10 days this is unlikely to have been a contributing factor. While proprioceptive stimuli from the thorax cannot be excluded, it appears likely that stimulation of pulmonary stretch-receptors was mainly responsible for the increased ventilatory drive.

A similar reflex hyperventilation is commonly seen in diffuse pulmonary fibrosis where hypoxaemia is mild or absent and PCO_2 low; Turino et al. (1963) concluded that increased stimuli from the abnormal lungs was responsible for the sustained overventilation in these cases. The mechanism in the present group of patients is

obscure. At 10 days clinical and radiological changes in the lungs were minimal or absent. It may be, however, that interstitial oedema or another lesion may have persisted to this relatively late stage.

It is also of interest to examine the way in which V_T and f combined to achieve the total ventilation at each stage (figure 11). The immediate effect of operation was a marked fall in V_T and increase of f. There was a further small rise in f up to 28 hr after operation. By 48 hr V_T had increased to almost the preoperative value, with little fall in f. By 10 days V_T was about the same but f was beginning to fall. These changes in f and V_T further suggest that stimulation of mechanoreceptors was the chief factor determining ventilatory behaviour following operation.

Dead space volume

Before this investigation was started it was expected that V_D would increase after operation as a result of increased $\dot{V}/\dot{Q}$ variance. Instead absolute dead space fell significantly. It should be noted that the V_D/V_T ratio (still a widely used criterion) increased, but this was due to the marked fall in V_T.

The reduction in absolute dead space suggests at least that $\dot{V}/\dot{Q}$ imbalance did not develop in the direction of underperfusion or overventilation, but this does not explain the reduction. As emphasized by Harris et al. (1973), correction of V_D for changes in V_T probably corrects, more or less, for changes in end-inspiratory position so long as FRC is reasonably constant. When FRC changes, V_T is no longer an adequate means of normalising V_D. Lifshay et al. (1971) found that V_D increases by an average of 26.7 ml for every litre increase in end-inspiratory volume. The end-inspiratory volume

in the patients can be calculated from FRC and V_T, and an estimate made of the change expected (according to Lifshay et al. 1971) in V_D at each stage. The results of such a calculation show expected reductions in V_D of 1.9, 6.9, 9.5 and 11.8% (mean 7.6%) at 8, 22, 28 and 48 hr compared with the preoperative value. The actual reductions were 9.1, 10.8, 15.0 and 8.8% (mean 10.9%). The correspondence is close enough to support the hypothesis that reduction in deadspace volume was mainly the result of change in end-inspiratory volume.

Arterial PCO_2 was generally higher when O_2 was breathed than when air was breathed (significant at 8 and 22 hr). As there was no significant change in $\dot{V}_E$ between air-breathing and O_2-breathing periods it seems a greater proportion of ventilation must have been wasted in the dead space when O_2 was breathed. Absolute V_D and V_D% were bigger when O_2 was breathed than during air-breathing (significant at 22 and 28 hr) and changes in V_T and f were not responsible for the difference. This rise in V_D might be related to the fall in $\dot{Q}t$, when O_2 is breathed, with a consequent increase in underperfused areas of lung. However the regression of change in cardiac index on change in V_D% gives a correlation coefficient of 0.0967, suggesting that this is not the mechanism. If, while breathing air, dependent areas of the lung are the most hypoxic, then breathing O_2 may release vasconstriction in these areas and lead to decreased upper zone perfusion with a subsequent increase in V_D. This was the mechanism suggested by Larson and Severinghaus (1962) and was discussed on page 20 and 32.

RVR and IAV

Although the RVR has been found clinically to be a useful

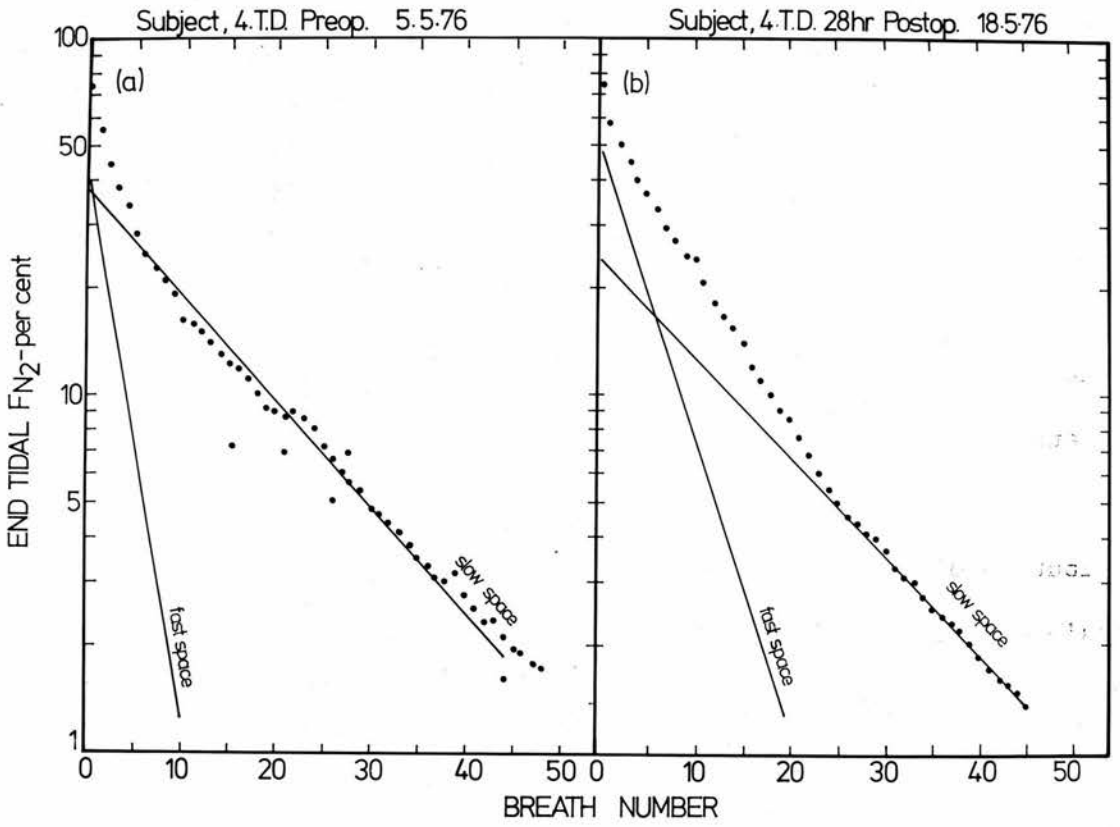


Figure 14. Spurious improvement of indices of inspired gas distribution following CPBP. Plots of end-tidal F_{N_2}, on a log scale, against breath number on a linear scale, for patient 4, (a) before operation and (b) 28 hr after operation. Lines characterising the fast and slow spaces are shown.

In (a) fast space r = 0.99683, slow space r = 0.99603, RVR = 11.83, IAV = 50.51, FRC = 1610 ml. In (b) fast space r = 0.9944, slow space r = 0.9998, RVR = 3.21, IAV = 58.61, FRC = 1370 ml.

Postoperatively the washout curve is almost a straight line as might be expected from a uniformly ventilated lung.

index of inspired gas distribution the assumptions made in its calculation are a potential source of error. The assumptions that may be inaccurate include: (1) the lung is characterised by two compartments; (2) end-tidal N_2-concentration reflects a true mixture of gas from both compartments; (3) tidal volume and frequency are constant through the washout; and (4) the contribution of N_2 from the fast space can be neglected over the last part of the curve. No allowance was made in this study for the elimination of N_2 from blood and tissues and this is a further potential source of error.

The change in RVR and IAV after CPBP indicated that distribution of inspired gas had improved. Clinically this seemed impossible. For RVR to diminish, Vf or ΔVs would have to increase, or Vs or ΔVf would have to decrease. Significant changes in ventilation after CPBP are more likely to occur in the slow space, so the postoperative fall in RVR is probably due to a fall in the volume of the slow space which contributes to ventilation. Since the fall in RVR coincided with the time at which FRC was lowest, $\dot{Q}_{Va}/\dot{Q}_t$ breathing O_2 highest and x-ray appearances of atelectasis greatest, it seems probable that atelectasis of the slow space was the cause of the fall in RVR. The latter would also account for the rise in IAV. This paradoxical improvement of indices of inspired gas distribution demonstrates the inability of N_2-washouts to "see" very poorly ventilated areas of lung (Nye, 1961). Figure 14 shows an example of the spurious improvement of RVR and IAV following CPBP.

Interestingly, the two patients (8 and 9) who started with low RVRs and high IAVs and had normal distribution of inspired gas preoperatively did not show the same loss of communicating slow space,

and their N_2 washouts did show the expected deterioration of inspired gas distribution after operation.

Functional residual capacity

The measurement of FRC by the addition of Vf and Vs derived from a N_2-washout curve is not conventional, and was made in this study because more standard methods would have been impracticable. The errors involved in the calculation of RVR apply also to the measurement of FRC by N_2 washout but, as shown in the section on calculations in subjects with normal RVR and IAV, the washout FRC is not very different from FRC as measured by body plethysmography. The patients in the present investigation also had plethysmographic measurements made (table 15) and FRC from these can be compared with the FRC derived from the preoperative N_2-washout, remembering that in them the latter was recorded in the supine position. The corresponding regression equation is:

FRC (plethysmograph) = 0.7467 x FRC (N_2-washout) + 1832 ml

with $r = 0.6416$, $2P < 0.05$. Thus, in this group, plethysmographic FRC was consistently higher than N_2-washout FRC by a mean value of 1276 ml ($2P < 0.001$). Part of this difference might be due to the different posture in which each was measured but this is unlikely to account for such a large difference. Whitfield et al. (1950) measured total lung volume and its subdivisions in both lying and sitting positions in 56 normal subjects aged from 10-70 yr. Functional residual capacity was determined by the closed-circuit hydrogen-dilution method; in some cases helium was used instead of hydrogen. Mean FRC, sitting was 2.933 l and lying 2.288, a mean difference of 644 ml. Several of the patients in the present study had evidence

of "small airways disease", and abnormal RVR and IAV, and it is probable that some of the difference between plethysmographic and washout FRC was due to trapped gas measured by the plethysmograph but not "seen" by the N_2-washout. Using the difference between plethysmographic FRC and N_2-washout FRC is an index of the preoperative volume of trapped gas the latter is found to be positively correlated with the postoperative change in air-breathing $\dot{Q}_{Va}/\dot{Q}_t$ ($r = 0.7166$, $2P < 0.05$) but not significantly with the change in $\dot{Q}_{Va}/\dot{Q}_t$ when O_2 is breathed.

Inasmuch as the N_2-washout does not "see" trapped gas or areas of lung with very low ventilation, the FRC so calculated is likely to indicate the volume of lung which is of functional importance in pulmonary blood-gas exchange. In this connection it is of interest that the per cent change in FRC postoperatively is significantly and negatively correlated with the actual increase in $\dot{Q}_{Va}/\dot{Q}_t$. This confirms results of Alexander et al. (1973) who showed that the same correlation of fall in FRC with postoperative increase in $\Delta AaPO_2$ holds for patients who had upper abdominal operations. In the latter study FRC was measured by the closed-circuit N_2 equilibration technique. These authors discussed the possible reasons for the reduction in FRC and concluded that compression of the lung by muscle spasm and abdominal distension caused a rise in transpulmonary pressure, smaller FRC and a greater degree of narrowing of small airways. Actual collapse of lung tissue and the increase in significant airway closure caused by the lung "splinting" (FRC became less than CC), was thought to be responsible for the hypoxaemia after abdominal surgery.

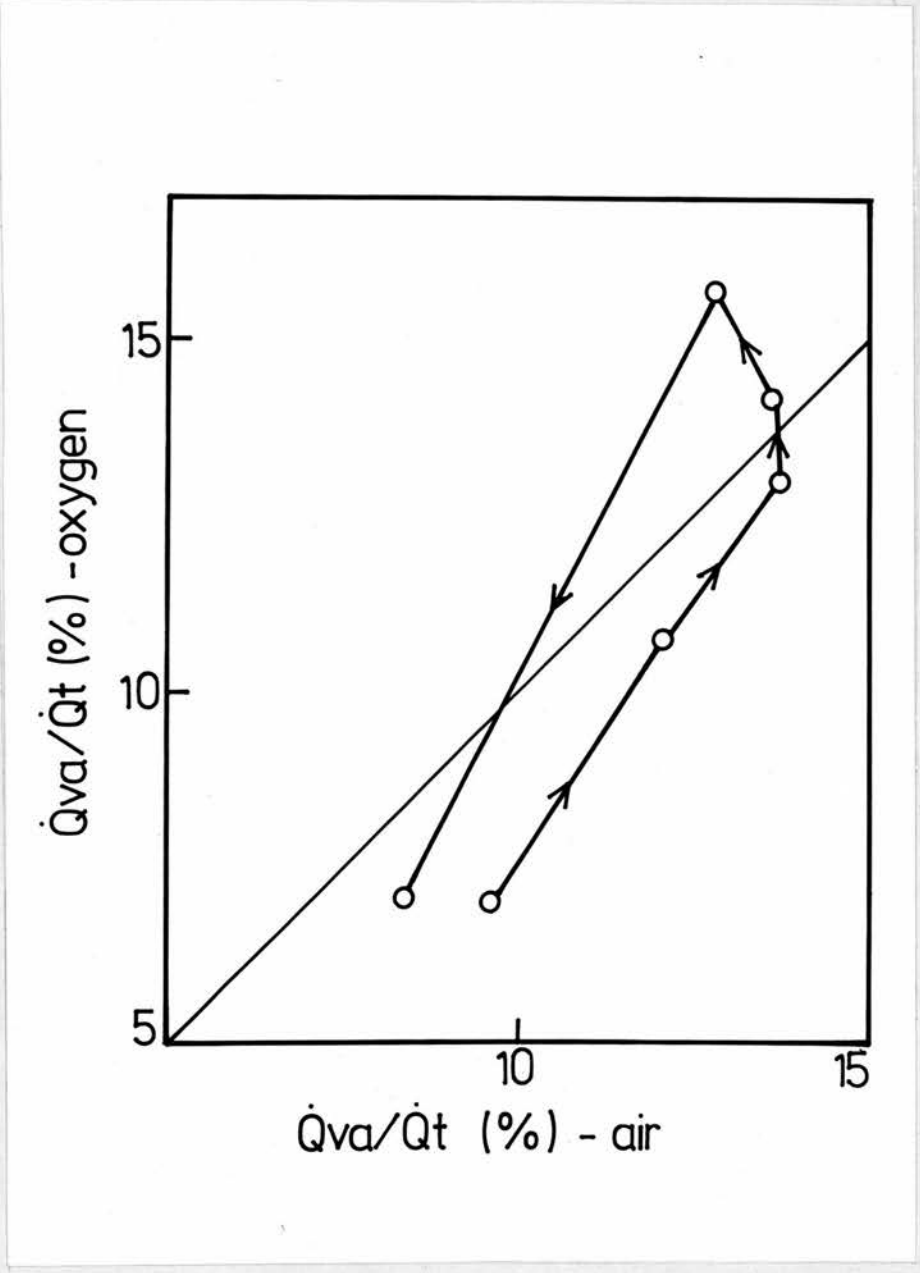


Figure 15. Mean values of $\dot{Q}va/\dot{Q}t$, while breathing air, plotted against $\dot{Q}va/\dot{Q}t$ while breathing O_2. Following the direction of the arrows indicates the results before operation and at 8, 22, 28, 48 hr and 10 days after operation. The line of identity is shown.

Venous admixture

Before operation mean values of venous admixture for the CPBP group were higher than those found in either group B or group C of our normal subjects. However of all the preoperative venous admixture measurements only one (patient 5, $\dot{Q}_{Va}/\dot{Q}_t$ breathing air) was outside the 95% confidence interval of the normal group. This suggest that β-adrenergic blockade may have had little effect in increasing $\dot{Q}_{Va}/\dot{Q}_t$ preoperatively. If it can be assumed that the admixture measured at 10 days represents the minimal value that will be reached after operation (this may be unjustified), then the similarity of $\dot{Q}_{Va}/\dot{Q}_t$ values at 10 days and preoperatively adds support to the suggestion that β-adrenergic blockade had little influence on venous admixture. From the review of the literature it seems that these findings would be in keeping with acute changes noted to follow infusion of propranolol. Stone et al. (1971) showed that in 10 patients with chronic bronchitis $\Delta AaPO_2$ was reduced after propranolol infusion. Assuming that $\Delta a\bar{v}C_{O2}$ would have been increased by the infusion (Hamer et al., 1965; Astrӧm, 1968) $\dot{V}/\dot{Q}$ relationships must have improved.

Both air-breathing and O_2-breathing venous admixture increased after CPBP. The increase of $\dot{Q}_{Va}/\dot{Q}_t$ was greater when O_2 was breathed than when air was breathed (figure 15). Venous admixture was bigger during O_2-breathing than during air-breathing at 28 and 48 hr. The high $\dot{Q}_{Va}/\dot{Q}_t$ when O_2 was breathed shows that admixture was due largely to intrapulmonary shunt and, since admixture was higher when O_2 was breathed then when air was breathed, areas of lung with critically low $\dot{V}/\dot{Q}$ ratio must have been extensive. The times at which O_2-breathing admixture was highest coincided with the times when

RVR and FRC were lowest and the chest x-rays showed subsegmental atelectasis. Actual collapse of lung tissue and increase in the amount of lung subjected to airway closure could produce areas of lung with no ventilation and areas with critically low $\dot{V}/\dot{Q}$ ratio. The probable importance of airway closure as a mechanism producing venous admixture is demonstrated again by the CPBP group in whom preoperatively, supine CV-ERV is closely correlated with both air- and O_2-breathing $\dot{Q}_{Va}/\dot{Q}_t$. The demonstration of significant numbers of alveoli which close when O_2 is breathed, in the early postoperative period, indicates that prolonged O_2-breathing might increase the likelihood of atelectasis at this time.

The lack of correlation between operative and preoperative factors, on the one hand, and the change in $\dot{Q}_{Va}/\dot{Q}_t$ after CPBP, on the other, is a little surprising. More surprising still is the observation that the size of admixture preoperatively is negatively correlated with the change in admixture after operation. Patients with high venous admixture before operation had less increase in $\dot{Q}_{Va}/\dot{Q}_t$ after operation than did patients who started with small $\dot{Q}_{Va}/\dot{Q}_t$s. By 48 hr it appears that most patients reached a similar maximum level of admixture (approximately 12% on air, and 15% on O_2) irrespective of the degree of admixture before operation. This might mean that there is a maximum tolerable admixture above which most "normal" subjects will compensate, for example by taking deeper breaths or coughing.

It is interesting to assess the potential error that would have arisen in the calculation of $\dot{Q}_{Va}/\dot{Q}_t$ had an arterio-venous O_2-content difference of 50 $ml.l^{-1}$ been assumed at all times throughout this study. An example is shown below for a patient who is

fairly representative of the group as a whole:

	$\dot{Q}_{Va}/\dot{Q}_t$ % (air-breathing)				
	Preop	8 hr	22 hr	28 hr	48 hr
$\Delta a\bar{v}C_{O2}$ Measured	2.09	6.28	9.25	13.18	16.45
" Assumed	1.54	8.20	12.88	15.79	20.30

Venous admixture would, therefore, have been overestimated at all times and the maximum error would have arisen at the 48 hr study when the real $\dot{Q}_{Va}/\dot{Q}_t$ would have been overestimated by 23%.

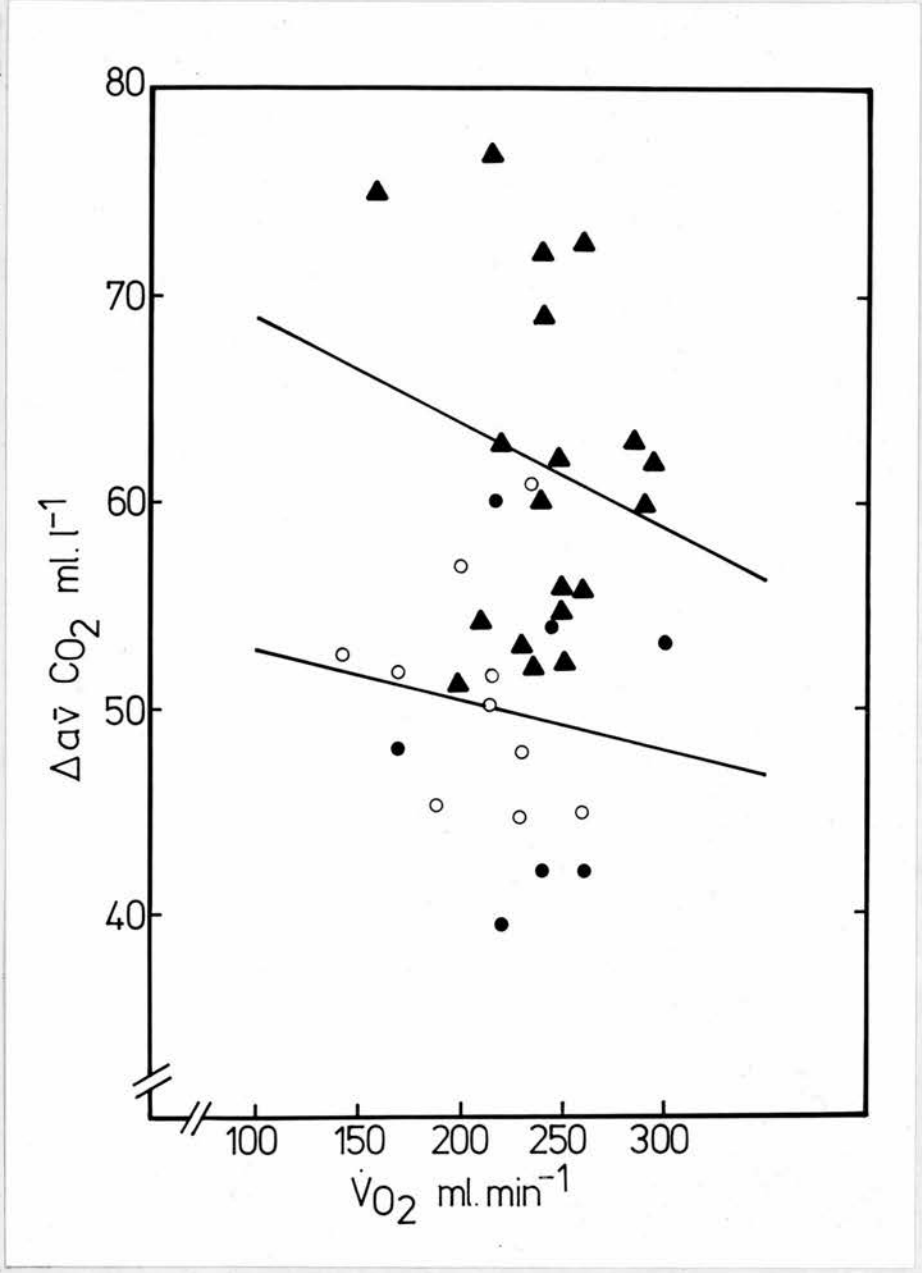


Figure 16. $\Delta a\bar{v}C_{O_2}$ plotted against $\dot{V}_{O_2}$. The lower continuous line is the regression for group 1, and the upper line for group 2. Group 1, values from the preoperative study (open circles) and from the study 10 days after operation (closed circles). Group 2, (closed triangles), values for the 22 and 28 hr post-operative studies.

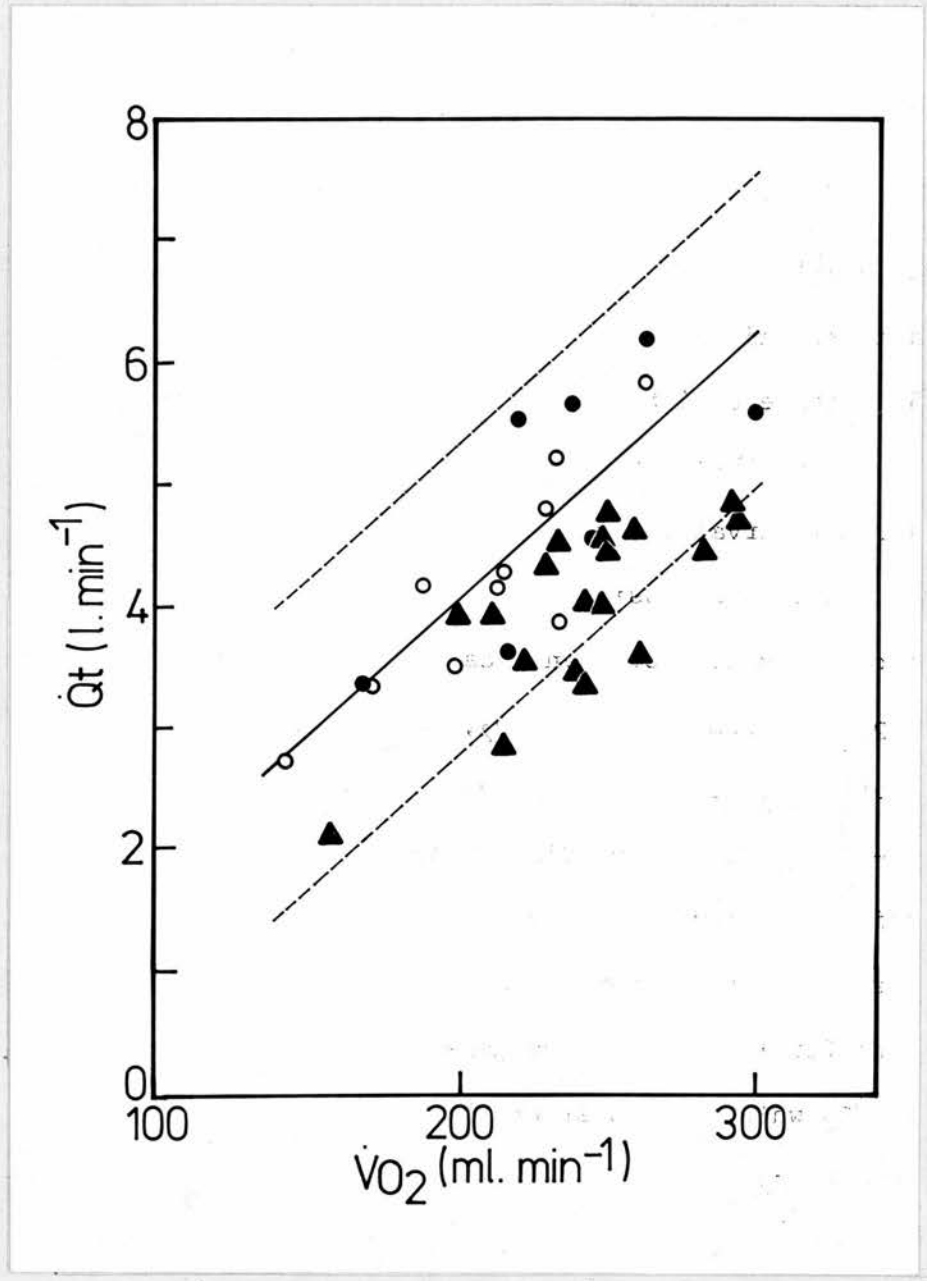


Figure 17. Cardiac output, breathing air, plotted against $\dot{V}_{O2}$. The regression line and 95%-confidence interval about regression for group 1 are shown. Group 1, values from the preoperative study (open circles) and from the study 10 days after operation (closed circles). Group 2, values from the 22, and 28 hr postoperative studies.

Cardiac output and $\Delta a\bar{v}C_{O_2}$

Figures 16 and 17 show $\Delta a\bar{v}C_{O_2}$ and $\dot{Q}_t$ plotted against $\dot{V}O_2$ for the preoperative, 22- 28 hr and 10-day studies. To look for changes caused by the operation the preoperative and 10-day post-operative values have been combined (group 1) and compared with the values at 22 and 28 hr (group 2). In figure 17 the regression line and 95% confidence interval about regression for group 1 are shown. It can be seen that many of the group 2 values lie below the 95%-confidence interval for group 1. In figure 16 $\Delta a\bar{v}C_{O_2}$ is plotted against $\dot{V}O_2$ and regression lines for the two groups are shown. Although the regressions are not significantly different it can be seen that in group 1 for all values of $\dot{V}O_2$, $\Delta a\bar{v}C_{O_2}$ is never greater than 60 $ml.l^{-1}$ while for the early postoperative values (group 2) many of the arterio-venous O_2-content differences are over 60 $ml.l^{-1}$. The regression for group 1 values of $\dot{Q}_t$ on $\dot{V}O_2$ suggests that a small increase in $\dot{V}O_2$ is ordinarily achieved by a rise in $\dot{Q}_t$ with $\Delta a\bar{v}C_{O_2}$ remaining fairly constant and generally below 60 $ml.l^{-1}$. The slight rise in $\dot{V}O_2$ which occurs after the operation is initially met in an abnormal way. There is no increase in $\dot{Q}_t$ but a significant rise in $\Delta a\bar{v}C_{O_2}$. By 10 days after the operation this has changed i.e. at 22 hr $\dot{V}O_2$ 235 $ml.min^{-1}$, $\dot{Q}_t$ 3.85 $l.min^{-1}$, $\Delta a\bar{v}C_{O_2}$ 62 $ml.l^{-1}$; at 10 days $\dot{V}O_2$ 236 $ml.min^{-1}$, $\dot{Q}_t$ 4.94 $l.min^{-1}$, $\Delta a\bar{v}C_{O_2}$ 48.5 $ml.l^{-1}$. Whether the unusual response to an increase of $\dot{V}O_2$ in the early postoperative period is due to the operation or to the effect of β-adrenergic blockade is uncertain. The cardiac output in this period may be termed inadequate or abnormal in so far as there is no increase of $\dot{Q}_t$ despite the rise in $\dot{V}O_2$. After CPBP the cardiac output in these patients seems to have been significantly depressed and

(as judged by $\Delta a\bar{v}C_{O_2}$) was inadequate at 22, 28 and 48 hr after operation. By 10 days $\Delta a\bar{v}C_{O_2}$ had fallen again and was not significantly different from the preoperative value.

The question arises as to how far β-blockade may have affected the cardiac output during the period of study. Preoperatively $\Delta a\bar{v}C_{O_2}$ was insignificantly higher than at 10 days, indicating that β-adrenergic blockade may not have had a very large effect on resting $\dot{Q}_t$ preoperatively. The similarity between the preoperative and the 10-day postoperative values and the difference of both from group 2 values suggest that the changes in $\dot{Q}_t$ and $\Delta a\bar{v}C_{O_2}$ were really due to the operation and/or CPBP and not to β-adrenergic blockade. Also the withdrawal of β-blockade would, if anything, tend to decrease $\Delta a\bar{v}C_{O_2}$ postoperatively, an effect opposite to that observed and opposite to that expected to follow cardiac operations with CPBP.

The inadequacy of $\dot{Q}_t$ following coronary vein graft operations is similar to that reported to follow repair of a variety of congenital and acquired cardiac defects by Kirklin and Theye (1963). These authors found that in 47 patients cardiac index averaged 3.2, 2.7 and 2.9 $l.min^{-1}.m^{-2}$, 4 hr, 2 and 3 days after operation, respectively. It is interesting that Kirklin and Theye showed the same time-course as that seen in the present study. $\dot{Q}_t$ was higher on the first and third than on the second postoperative day.

Cardiac output fell and $\Delta a\bar{v}C_{O_2}$ rose in all the studies when O_2 was breathed. The mean air-breathing $\Delta a\bar{v}C_{O_2}$ for all values was 56.0 $ml.l^{-1}$ and for all O_2-breathing values 59.5 $ml.l^{-1}$ ($2P < 0.001$). This 6% increase in $\Delta a\bar{v}C_{O_2}$ when O_2 is breathed is in

keeping with the change in $\dot{Q}_t$ (measured by ballistocardiogram) reported by Dripps and Comroe (1947) and Whitehorn et al. (1946) in normal subjects. It is at variance with the insignificant change in directly measured $\Delta a\bar{v}C_{O2}$ reported by Barratt-Boyes and Wood (1958) in 20 normal subjects. In the present study the fall in $\dot{Q}_t$ that follows a change in air-breathing to breathing O_2 becomes small and insignificant in the early postoperative period, and is least when the $\dot{Q}_t$ is lowest (figure 12). This again confirms the results of Kirklin and Theye (1963) who reported no consistent change in $\dot{Q}_t$ when O_2-breathing was changed to air-breathing in the early postoperative period. Eltringham et al. (1968) noted a rise in $\Delta a\bar{v}C_{O2}$ from 53.7 (SD 10) to 60.1 (SD 10) $ml.l^{-1}$ on changing from air- to O_2-breathing in 60 measurements made after CPBP. The exact times after operation at which these measurements were made are not reported. Neither the fall in $\dot{Q}_t$ when O_2 is breathed nor the reduction in this effect after operation can be attributed to β-adrenergic blockade, since the preoperative and 10-day postoperative air-O_2 differences are quite similar.

What happens to cardiac output when O_2 is breathed has not been established with certainty. Undoubtedly in the patients in this study $\dot{Q}_t$, measured by the Fick method, falls when air-breathing is changed to O_2 ($\dot{V}O_2$ is assumed to be the same during O_2-breathing as that measured during air-breathing). The patients of the present study, having severe coronary artery disease, may behave differently, in this respect, from healthy subjects. Another question raised by the present results is why the air-O_2 change in $\dot{Q}_t$ should become insignificantly small in the early period after operation. It is as if the patients' hearts had become unable, for a while, to respond to whatever stimulus produces the air-O_2 change.

Factors influencing the deterioration of $\dot{Q}_{Va}/\dot{Q}_t$ and $\Delta a\bar{v}C_{O_2}$ after CPBP

Conflicting views have been expressed about the influence of various operative factors on the degree of postoperative deterioration in pulmonary blood gas exchange and cardiac output. Fordham (1965) found no correlation between the degree of postoperative hypoxaemia and the duration of bypass. Turnbull et al. (1974) found that in individual patients the fall in Pa_{O_2} was related to the length of time on CPBP. Provan et al. (1966) in their study of the clinical incidence of pulmonary complications after CPBP concluded that the duration of the operation was more important than the duration of perfusion in causing postoperative respiratory complications.

In the present investigation no clinical factor seems to have had any striking influence on the degree of deterioration after CPBP. Only the preoperative LVEDP comes close to a significantly positive correlation with the postoperative increase in $\dot{Q}_{Va}/\dot{Q}_t$. Neither total operation time nor length of perfusion seems to have been related. The significantly negative correlation of preoperative admixture with the postoperative changes had been discussed. The patients with high $\Delta a\bar{v}C_{O_2}$ before operation had the highest at 48 hr and 10 days ($r = 0.5620$ and $r = 0.4995$, both $2P < 0.05$), but the preoperative value of $\Delta a\bar{v}C_{O_2}$ was not correlated with the postoperative change. A low left ventricular ejection fraction, long operation time and long bypass time were positively related to the postoperative increase in $\Delta a\bar{v}C_{O_2}$, but none of these correlations is significant. The lack of statistical significance is not surprising with such small numbers of observations and some of these suggested trends may be of importance.

Preoperative LVEDP, ejection fraction, the operative time, bypass time, aortic clamp time and the amount of cross-matched blood given have all been tested for a correlation with the highest $\dot{Q}_{Va}/\dot{Q}_t$ and $\Delta a\bar{v}CO_2$ reached after CPBP. None of these correlations is significant.

Comparison with other studies

Tables 35, 36 and 37 summarise the data for venous admixture, arterial O_2-tension and, alveolar-to-arterial O_2-tension differences reported, by other workers, to follow CPBP, and allow a comparison to be made with the results of the present study. The other studies have been described in the review of the literature. The results of Eltringham et al. (1968), Turnbull et al. (1974) and Philbin et al. (1970) probably provide the best comparison with the present study, but as discussed previously differences in patients, bypass technique and methods of measurement, make comparison of limited value. The patients of Eltringham et al. (1968) had pulmonary hypertension and R was assumed in the calculation of PAO_2. Turnbull et al. (1974) did not measure $\dot{Q}_{Va}/\dot{Q}_t$ and assumed that end-tidal O_2 and CO_2 concentrations were equal to alveolar concentrations. Preoperative $\dot{Q}_{Va}/\dot{Q}_t$ breathing air was much higher in the present study than in that of Philbin et al. (1970) and both the per cent and absolute increase after CPBP much less. Admixture when breathing O_2 was also lower before operation in the patients of Philbin et al. (1970) and although their per cent increases after CPBP were bigger, the absolute increases at 24 and 48 hr were similar to those found in this series. The changes in $\dot{Q}_{Va}/\dot{Q}_t$, when O_2 is breathed, reported for the present study are also within the range reported by Eltringham

Table 35. Venous admixture ($\dot{Q}va/\dot{Q}t$ %): comparison of present data with previous studies of cardiopulmonary bypass.

Reference	Number of patients	Operation	Age range (yr)	Preoperative Mean	Preoperative Range or SD	Postoperative 2 - 8 hr Mean	2 - 8 hr Range or SD	2 - 8 hr Δ%	24 hr Mean	24 hr Range or SD	24 hr Δ%	48 hr Mean	48 hr Range or SD	48 hr Δ%	72 hr Mean	72 hr Range or SD	72 hr Δ%	10days-3weeks Mean	10days-3weeks Range or SD	10days-3weeks Δ%
Air-breathing																				
Hedley-Whyte et al.(1965)	7	AV	42-71						15.5	0.7	-									
	6	MV	47-62						26.2	1.7	-									
McClenahan et al.(1965)	8	AV3 ASD1 OC3 VSD1	16-36	2.8	1.8-4.4	21.4	8.9-33	+664	21.1	3.1-31	+654	23.8	3.8-46	+750				3.6	0-12.0	+29
Fordham (1965)	12	AV	-			16.5	5.0	-	23.5	10.6	-	28.2	7.0	-	25.2	4.7	-			
Philbin et al. (1970)	14	MV10 AV4	23-68	5.3	3.4	18.1	13.1	+242	19.7	10.0	+272	17.1	9.3	+223						
Present study	10	CVG	40-68	9.59	5.56	12.07	4.12	+26	13.71	6.40	+43	12.81	2.90	+34				8.36	2.80	-13
Oxygen-breathing																				
Hedley-Whyte et al.(1965)	7	AV	42-71						14.2	1.7	-									
	6	MV	47-62						13.7	2.1	-									
McClenahan et al.(1965)	8	AV3 ASD1 OC3 VSD1	16-36	4.4	2.2-7.5	12.0	3.8-21	+173	16.2	6.7-22	+268	19.3	11-39	+339				-	4.3-8.4	-
Philbin et al. (1970)	14	MV10 AV4	23-68	3.85	5.3	13.43	10.1	+249	8.9	4.8	+131	9.1	4.2	+136						
Eltringham et al.(1968)	12	MV	30-69	4.75	2.9				9.1	4.8	+92	8.5	2.8	+79	8.6	2.8	+81	4.7	1.5	-1
Present study	10	CVG	40-68	7.02	2.45	10.77	4.82	+53	13.01	4.07	+85	15.71	4.78	+124				7.07	3.57	+1

AV, aortic valve replacement or repair; MV, mitral valve replacement; OC, occlusive cardiomyopathy; ASD, repair of atrial septal defect; VSD, repair of ventricular septal defect; CVG, coronary-vein graft; Δ%, $\frac{\text{postoperative value - preoperative value}}{\text{preoperative value}} \times 100$

Table 36. Arterial O_2-tension (Pa_{O_2}, mm Hg): comparison of present data with previous studies of cardiopulmonary bypass.

Reference	Number of patients	Operation	Age range (yr)	Preoperative Mean	Preoperative Range or SD	Postoperative 2 - 8 hr Mean	2 - 8 hr Range or SD	2 - 8 hr Δ%	24 hr Mean	24 hr Range or SD	24 hr Δ%	48 hr Mean	48 hr Range or SD	48 hr Δ%	72 hr Mean	72 hr Range or SD	72 hr Δ%	10 days-3 weeks Mean	10 days-3 weeks Range or SD	10 days-3 weeks Δ%
Air-breathing																				
Hedley-Whyte et al.(1965)	7	AV	42-71						65	10.3										
	6	MV	47-62						53	7.6										
Fordham (1965)	12	AV	-	87	10.5	64	11.0	-26	56	10.1	-36	57	6.8	-34	62	6.7	-29			
Philbin et al. (1970)	14	MV10 AV4	23-68	84.8	13.5	59.5	10.9	-30	58.2	8.7	-31	55.0	12.2	-35						
Eltringham et al.(1968)	12	MV	30-69	77.0	10.8				60.5	7.9	-21	60.4	9.6	-22	63.1	11.8	-18	78.8	10.1	+2
Turnbull et al. (1974)	19	CVG17 AMV2	30-64	91.5	2.79				70.5	2.56	-23	71.8	2.65	-22	70.4	2.06	-23			
Present study	10	CVG	40-68	72.8	9.95	66.6	7.86	-9	62.1	8.61	-15	62.1	4.47	-15				72.0	5.11	-1
Oxygen-breathing																				
Hedley-Whyte et al.(1965)	7	AV	42-71						319	116										
	6	MV	47-62						324	133										
Eltringham et al.(1968)	12	MV	30-69	585	31				447	105	-24	476	62	-19	492	60	-16	596	29	+2
Turnbull et al. (1974)	19	CVG17 AMV2	30-64	510	17.6				276	24.6	-46				331	23.8	-35			
Geha et al. (1966)	16	(MV	Mean 45	417	320-512	293	176-430	-30	311	209-395	-25	254	115-308	-39				352	312-395	-16
		(AV	Mean 49	413	352-489	319	172-385	-23	275	231-329	-33	217	110-343	-47				350	237-432	-15
Present study	10	CVG	40-68	526	52.3	447	77.9	-15	361	86.5	-31	314	101	-40				539	53.7	+2

AMV, aortic and mitral valve replacement; symbols otherwise as in Table 35.

Tabel 37. Alveolar-to-arterial O_2-tension difference (ΔAaP_{O_2}, mm Hg): comparison of present data with previous studies of cardiopulmonary bypass.

Reference	Number of patients	Operation	Age range (yr)	Preoperative Mean	Preoperative Range or SD	2 - 8 hr Mean	2 - 8 hr Range or SD	2 - 8 hr Δ%	24 hr Mean	24 hr Range or SD	24 hr Δ%	48 hr Mean	48 hr Range or SD	48 hr Δ%	72 hr Mean	72 hr Range or SD	72 hr Δ%	10 days-3 weeks Mean	10 days-3 weeks Range or SD	10 days-3 weeks Δ%
Air-breathing																				
Hedley-Whyte et al.(1965)	7	AV	42-71						36											
	6	MV	47-62						51											
McClenahan et al.(1965)	8	AV3 ASD1 OC3 VSD1	16-36	8	4-17	33	12-51	+313	36	8-46	+350	40	7-77	+400				7	0-22	-13
Fordham (1965)	12	AV	-	15	9.5	37	14.6	+147	48	11.1	+220	52	8.1	+247	49	9.5	+227			
Philbin et al.(1970)	14	MV10 AV4	23-68	27.7	12.3	55.2	13.1	+99	48.8	9.4	+76	56.2	9.1	+103						
Eltringham et al.(1968)	12	MV	30-69	27.6	11.3				40.5	12.4	+47	43.4	11.1	+57	44.2	11.0	+60	24.8	10.5	-10
Turnbull et al. (1974)	19	CVG17 AMV2	30-64	12.7	3.68				40.2	2.58	+217				38.5	2.20	+203			
Present study	10	CVG	40-68	20.7	9.59	31.1	11.6	+50	38.0	11.5	+84	39.5	10.6	+91				27.5	5.52	+33
Oxygen-breathing																				
Hedley-Whyte et al.(1965)	7	AV	42-71						350											
	6	MV	47-62						345											
McClenahan et al.(1965)	8	AV3 ASD1 OC3 VSD1	16-36	79	42-136	236	66-442	+199	326	121-465	+313	357	207-611	+352				-	76-153	-
Eltringham et al.(1968)	12	MV	30-69	87.5	29.0				214	117	+145	194	66	+122	185	60	+111	80.4	26	-8
Turnbull et al. (1974)	19	CVG17 AMV2	30-64	130	14.8				359	19.9	+176				323	18.9	+148			
Present study	10	CVG	40-68	140	57.5	215	79.3	+54	301	88.0	+115	350	107	+150				130	56.9	-7

Symbols as in Tables 35 and 36.

et al. (1968) and both these studies and the study of Philbin et al. (1970) report considerably less change than did McClenahan et al. (1965), who assumed a constant $\Delta a\bar{v}C_{O2}$. Per cent and absolute changes in $\Delta AaPO_2$ reported in the present study are similar to those reported by Philbin et al. (1970) and Eltringham et al. (1968) and considerably less than those reported by Fordham (1965), McClenahan et al. (1965) and Turnbull et al. (1974). In trying to account for these differences the influence of varying $\Delta a\bar{v}C_{O2}$ on $\Delta AaPO_2$ must be considered, as must the high incidence of respiratory complications in Fordham's patients and the use of end-tidal sampling by Turnbull et al. (1974). It is also worth noting that in these three studies mean $\Delta AaPO_2$ was quite low before operation and the large absolute increases after CPBP are consistent with the findings of the present study.

Values of PaO_2 before and after upper abdominal surgical procedures, reported in previous studies, are listed in table 38. They provide a comparison with the changes in PaO_2 found in the present study. The fall in PaO_2 during air-breathing reported by Siler et al. (1974), Knudsen (1970) and Gordh et al. (1958) is similar to that reported in this study. Reduction in O_2-breathing PaO_2 in the present study is similar to that described by Diament and Palmer (1967), and by Gordh et al. (1958) in their BNS anaesthesia group. On this evidence it seems that the fall in PaO_2 following CPBP is not greater than that which may be expected to follow upper abdominal operations.

Table 38. Arterial O_2-tension (Pa_{O2}, mm Hg): comparison of present data with previous studies of upper-abdominal surgical procedures.

Reference	Comments	No. of Patients	Mean Age (yr)	Preoperative	Postoperative Day 1	Postoperative Day 2	Postoperative Day 5+
Air-breathing							
Gordh et al. (1958)	BNS Anesthesia	14	-	80.6(11.3)	70.8(15.9)		
	Ether "	5	-	88.6(17.3)	76.6(14.7)		
	Spinal "	7	-	82.4(21.1)	75.0(16.9)		
Palmer & Gardiner (1964)	Partial gastrectomy	14	48	89.3	76.5	74.6	76.7
	" " + atelectasis	18	46	90.1	66.6	63.3	73.0
Diament & Palmer(1966)		64	52	92.4(13.3)	73.8(10.9)		
Knudsen (1970)	Upper abdominal (stomach)	8	67	89.3(8.75)	78.9(13.4)		87.8(7.52)
	Transthoracic (oesophagus)	8	61	91.0(6.59)	78.2(5.56)		79.1(5.11)
Alexander & Spence (1973)		101	43	86.3(9.25)	69.9(10.3)	71.0(11.7)	82.2(11.1)
Siler et al. (1974)		20	46	83 (8.94)	72 (13.4)		80 (8.94)
Present study		10	53	72.8(9.95)	62.1(8.61)	62.1(4.47)	72.0(5.11)
O_2-breathing							
Gordh et al. (1958)	BNS Anesthesia	14	-	529(86.4)	345(174)		
	Ether "	5	-	541(80.8)	453(113)		
	Spinal "	7	-	540(87.0)	450(79.6)		
Diament & Palmer(1967)		23	50	540(137)	360(155)		
Siler et al. (1974)		20	46	579(62.6)	476(112)		537(67.1)
Present study		10	53	526(52.3)	361(86.5)		539(53.7)

BNS, barbiturate-nitrous oxide-succinylcholine.

Mean values, with standard deviations in brackets.

Summary and conclusions

The smallest change in pulmonary function likely to follow CPBP, as practised at Green Lane Hospital in 1976, has been measured. Mean air-breathing $\dot{Q}_{Va}/\dot{Q}_t$ increased from 9.59% to reach a maximum of 13.71%, 22 hr after CPBP. Mean O_2-breathing $\dot{Q}_{Va}/\dot{Q}_t$ increased from 7.02% to reach a maximum of 15.71%, 48 hr after the operation. Ten days after the operation both had returned to the preoperative level. The increase in venous admixture would have been overestimated if an $\Delta a\bar{v}C_{O2}$ of 50 ml. $l.^{-1}$ had been assumed for the study. The admixture when O_2 is breathed shows that most of the deterioration in pulmonary blood-gas exchange is due to increase in regions of lung with no ventilation or critically low $\dot{V}/\dot{Q}$ ratio. The invasion of the tidal breathing level by airway closure, due to the fall in FRC, may mean that these areas have a contribution from airways subjected to continuous or cyclical airway closure. Neither the preoperative state of these patients nor the duration of CPBP afforded a reliable forecast of the degree of admixture to be expected after operation. Patients with a high $\dot{Q}_{Va}/\dot{Q}_t$ before operation had less increase of $\dot{Q}_{Va}/\dot{Q}_t$ after CPBP than did those with low admixtures preoperatively. In only one patient did PaO_2 fall below 50 mm Hg at any time after CPBP. Assisted ventilation is not generally required after coronary vein graft operations with CPBP. Excessive O_2-enrichment of inspired air may increase the incidence and extent of atelectasis postoperatively.

Cardiac output did not rise significantly in the early postoperative period despite the increase in oxygen uptake. There was therefore a rise in $\Delta a\bar{v}C_{O2}$. The latter was significantly higher than preoperatively by 22 hr after the operation and still raised, though less so, by 48 hr. The raised $\Delta a\bar{v}C_{O2}$ probably indicates

inadequacy of cardiac output during this period or at least a change in the way O_2 requirements are met. This change may be due to the operation rather than an effect of β-adrenergic blockade. A low left ventricular ejection fraction before the operation and a long operation and bypass time may be related to the postoperative increase in $\Delta\bar{a}\bar{v}C_{O_2}$. Coronary vein-graft operations with modern CPBP techniques produce no greater a fall in PaO_2 after operation than do upper abdominal surgical procedures without CPBP.

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